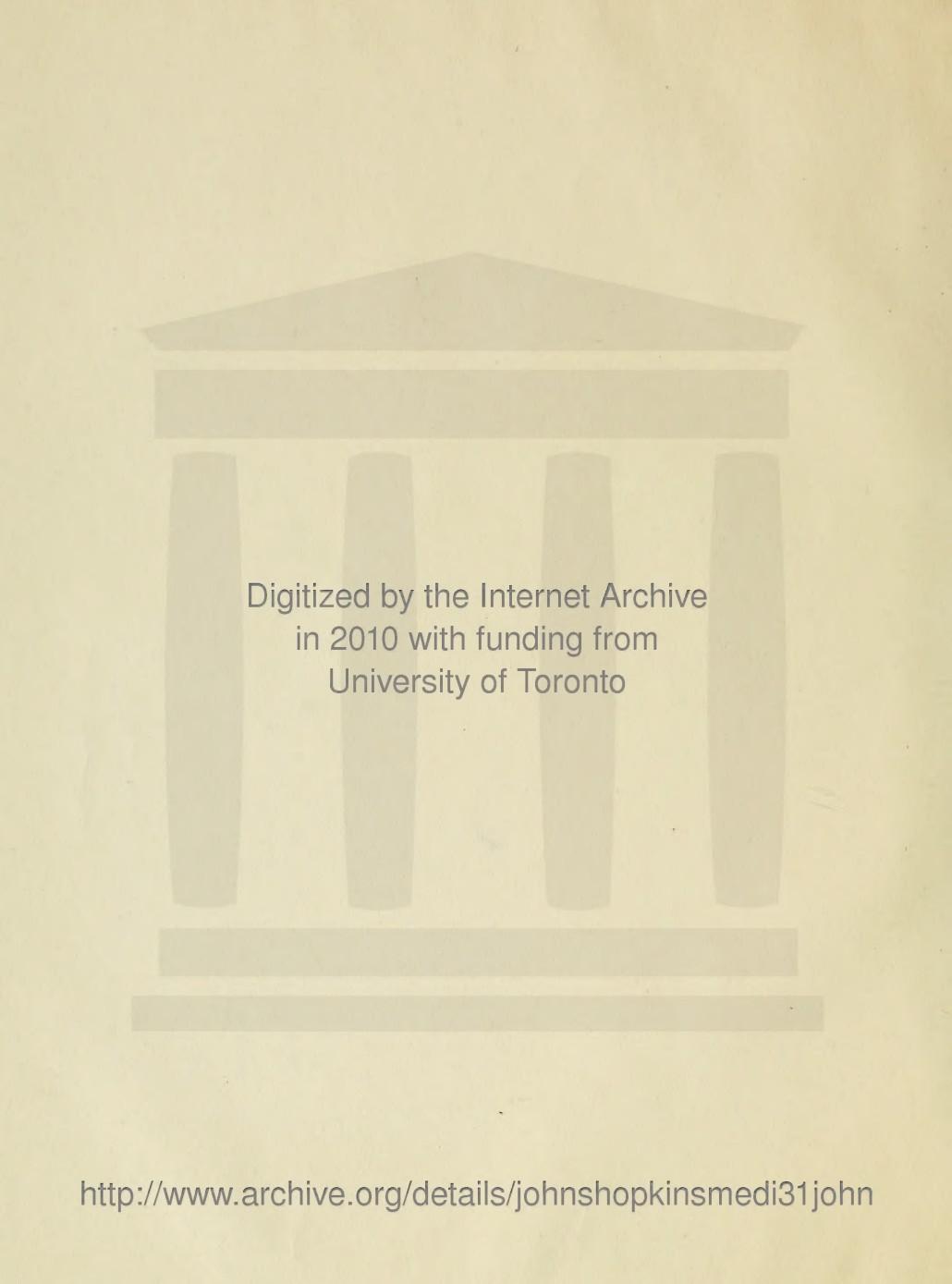






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BULLETIN



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# BULLETIN

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### THE EFFECT OF PYLORIC OBSTRUCTION IN RELATION TO GASTRIC TETANY\*

By W. G. MACCALLUM, JOSEPH LINTZ, H. N. VERMILYVE,  
T. H. LEGGETT, and E. BOAS

(From the Pathological Departments of Columbia University and The Johns Hopkins University)

The nature of gastric tetany has long been a matter of interest and the theories already advanced to account for it are quite unsatisfactory. According to one it is due to desiccation of the tissues, whereas another ascribes it to the absorption of toxic materials from the stagnating contents of the

\* These experiments were begun in 1909 in Baltimore, where all the effects of pyloric obstruction and of the administration of chlorides and hydrochloric acid were observed. They were resumed later with more accurate quantitative measurements in New York.

They were described, practically as they now appear, at the meeting of the American Society for Experimental Pathology held in New York with the Federation of Biological Associations at Cornell University Medical School in January, 1917, but various circumstances connected with my leaving New York for Baltimore and the press of work during the war have delayed their publication up to the present. In the meanwhile a paper by W. S. McCann has appeared in the *Journal of Biological Chemistry*, 1918, xxxv, 553, which describes quite similar experiments and results but with a somewhat different interpretation. (W. G. M.)

dilated stomach. It is known that if a communication be established between the stomach and the intestine by a gastro-enterostomy so that the contents of the stomach can once more pass into the intestine, the symptoms disappear at once. It was with the desire of determining the nature of the changes produced by pyloric obstruction that the following experiments were carried out. But, although they give clear evidence that a certain chain of events follows such an obstruction, they do not necessarily give an explanation of gastric tetany in the human being, and we have had no opportunity to make the same observations on man.

It was observed long ago (1909) by one of us (MacCallum) that when the pylorus was completely obstructed and the stomach frequently washed out, an animal wasted rapidly and died in a few days, usually with violent convulsions which were not precisely of the same character as the twitchings seen in parathyroid tetany.

We held the idea at that time that, since nothing was absorbed from the stomach, while water was given abundantly through the intestine, the older explanations offered for gastric tetany were faulty and that the convulsions must be due to loss of hydrochloric acid in the gastric juice. Later experiments have supported this view and we have tried to work out the nature of the whole disturbance.

Although many different methods have been employed from time to time in the attempt to obstruct the pylorus partially or completely we finally returned to the simplest, which consists in cutting through the stomach just above the pylorus and closing it off with sutures so that it becomes a blind sac on the end of the esophagus. The pyloric end with the duodenum was then brought into the abdominal wound and sutured there. Through it food and water were given, but in the later experiments, in order to eliminate all intake of chlorides and to prevent loss of bile and intestinal contents, this opening was closed except for a tube through which distilled water was introduced. The food which could be given in this way always contained chlorides and when it was given the symptoms following pyloric obstruction appeared only slowly so that the animal lived about a week. When nothing but water was given, convulsions appeared in about 48 hours and death soon followed. Such a result could not be due to starvation, because a dog will live a long time without food.

It is unfortunate that our observations upon the daily intake and output of chlorides are not more complete, but they are sufficient to show that under the conditions of the operation, even when no chlorides are given in the food, the obstructed stomach continues to secrete hydrochloric acid. Estimation of the chlorides in the stomach washings show that a considerable amount is lost to the body and this must be sufficient, in the absence of any intake, to lower the chlorides of the body rapidly. Indeed it is difficult to devise any other way in which such an abstraction of chlorides could be attained since the tissues ordinarily hold tenaciously to their chloride content when the intake is decreased. It seems that the gastric mucosa can still exercise its function of secreting hydrochloric acid even when the plasma chlorides are diminished.

**6709.** Pylorus obstructed May 6, 1909. Animal fed through intestinal fistula with sugar and beef together with distilled water. Six days later, May 12, violent twitching and stiffness, flexor spasm of fore feet and rigid clinching of jaws. Toward the end of the experiment sodium chloride was injected intravenously and relieved the twitching. Chlorides estimated in the washings from the stomach as follows:

6709 Chlorides as NaCl	May							
	6	7	8	9	10	11	12	13
Gastric fluid.....	1.56	3.0	3.3	.42	.....	.....	.....	.....
Urine .....	.27	.56	.22	1.6	.65	1.9	.....	.....

**6909.** Pylorus obstructed May 18, 1909. Animal fed as above with washed beef, sugar and water. Well until May 23, when

there was violent twitching of all the muscles. Was given calcium lactate intravenously which diminished the twitching.

6909 Chlorides as NaCl	May					
	18	19	20	21	22	23
Gastric fluid.....	.....	5.37	4.8	2.7	2.6	.....
Urine .....	.....	.....	2.2	1.6	.72	3.2

**6309.** Pylorus obstructed April 22, 1909. Fed with capsules of dried washed beef (chloride free) and water. Slight twitching beginning April 27. Was given sodium chloride intravenously. Died late next night.

6309 Chlorides as NaCl	April					
	22	23	24	25	26	27
Gastric fluid.....	.....	.....	1.7	3.07	3.1	1.4
Urine .....	.....	.....	2.7	.6	....	....

These observations show that the loss of chlorides from the stomach was continued for days after the operation. The excretion in the urine tended to decrease day by day after the operation. Later when we had found that the analysis of the blood plasma showed more directly and more precisely the changes in the chlorides, we made these determinations every day and ceased to analyze stomach washings and excreta for chlorides.

Since the chloride lost in the gastric juice is in the form of free hydrochloric acid, it seemed probable that the sodium ion would be retained in the circulating fluids and that the alkali reserve of the blood might be increased.

In the next series of experiments, therefore, we studied the changes in the plasma chlorides, the alkali reserve as determined by Van Slyke's method and the electrical excitability of the nerves.

In brief we found that, especially in those cases in which no chlorides were given by the intestinal fistula, the recognizable chlorides in the plasma dropped rapidly. The average course taken from 12 cases was as follows, beginning with the day of the operation: 6.6, 6.4, 5.1, 4.6, 3.9, but in some cases the chloride content of the plasma fell to 2.5 or 2.8.

The carbon dioxide combining power was found to rise as the chlorides decreased. Averaging once more eight cases in which this is tabulated we find that the change proceeds as follows, beginning with the day of operation: 46.2, 42.4, 55.2, 61.1, 66.6, 71.9, 74.7, 80 (volume in c. c. per 100 c. c. blood). It is hardly possible to average the records of the electrical excitability, but an approximation was made in six cases by adding the figures KC, KO, AC and AO into one figure for each observation. Then if these figures be averaged for the series of animals beginning with the day of operation they run as follows: 7.6, 7.1, 4.5, 2.8, in which of course the lowest number represents the lowest current necessary and therefore the highest excitability.

The following are illustrative protocols:

1605. Pylorus obstructed October 30, 1916. Animal fed through the intestinal fistula with milk and eggs; developed distinct tetany-like twitchings on November 6, followed by violent convulsions and death. During this time the dog's weight sank from 7630 grams to 6210 grams. Electrical excitability was very distinctly heightened. The plasma chlorides sank.

1605	October		November					
	30	31	1	2	3	4	5	6
Electrical excitability	Operation						Tetany	
	KC	0.2	0.2	0.05			0.05	
	KO	Neg. 5	Neg. 5	Neg. 5			1.2	
	AC	1.0	0.4	0.4			0.4	
Plasma chlorides	AO	1.0	1.2	1.2			0.4	
		6.41	5.67	5.67			4.10	

1609. Pylorus obstructed November 24, 1916. Fed through fistula with milk and eggs. On November 27, distinct tetanic twitchings were developed with high electrical excitability. An intravenous injection of 35 c. c. of 10% NaCl was given which relieved the twitchings but these reappeared the next day and the dog died.

1609	November					
	23	24	25	26	27	28
Electrical excitability	Pyloric obstruction			NaCl		
	KC	0.3	0.2	0.15	0.30	0.4
	KO	Neg. 5	Neg. 5	1.4	3.6	2.2
	AC	1.2	0.8	0.8	0.71	3.0
Plasma chlorides	AO	1.4	1.6	0.4	1.22	5.1
		7.4	5.43	4.9	6.45	5.3
Total NaCl intake	1.20	1.24	1.31	1.33	3.95	Neg. Bal.
Total NaCl output	2.11	1.30	5.33	2.81	2.92	5.44

1612. After a preliminary operation to establish an intestinal fistula on Dec. 2, 1916, the pylorus was obstructed on December 8. The dog lived until Dec. 14. There was nothing resembling tetany but observations on the chlorides and the alkali reserve are recorded. The animal was fed with milk, eggs and sugar.

1612	December						
	7	8	9	10	11	12	13
Electrical excitability	KC	0.2	0.3	0.3	0.2	0.3	0.3
	KO	Neg. 5	3.0				
	AC	1.2	1.4	1.4	1.0	1.2	1.2
	AO	2.6	2.8	2.4	2.0	2.0	1.8
Plasma chlorides	..	6.6	6.7	6.8	5.7	5.4	4.7
CO <sub>2</sub> combining power (vols. in c.c. per 100 c.c. of blood)	..	49.0	58.6	62.4	61.4	63.3	74.9
Total NaCl intake	1.43	1.27	1.34	1.28	1.1	1.1	1.06
Total NaCl output	1.48	0.75	3.09	0.2	1.48	....	2.14

1618. Pyloric obstruction December 14, 1916. Given distilled water only through intestinal fistula; developed distinct and continuous twitchings on December 16 and died.

1618	December			
	14	15	16	
Electrical excitability	KC	....	0.2	0.2
	KO	....	Neg. 5	Neg. 5
	AC	....	0.8	1.0
	AO	....	1.4	1.8
Plasma chlorides	....	6.6	6.7	5.5
CO <sub>2</sub> combining power	....	46.7	39.1	33.1

1620. Pylorus obstructed December 17, 1916. Dog given distilled water only through intestine. Violent convolution with opisthotonus on December 19. Electrical excitability greatly increased, plasma chlorides diminished. Alkali reserve not greatly heightened. Given 50 c. c. of 1% HCl intravenously. This lowered the alkali reserve but scarcely affected the electrical excitability. Died about four hours later.

1620	December			
	17	18	19	
Electrical excitability	KC	0.2	0.2	0.1 ↓ 0.3
	KO	Neg. 5	Neg. 5	1.6 1.8
	AC	1.0	1.0	0.8 0.6
	AO	1.4	0.4	1.2 0.8
Plasma chlorides	....	7.2	5.63	5.22
CO <sub>2</sub> combining power	....	41.15	38.2	35.7 30.7 47.5

1621. Pylorus obstructed December 18, 1916. Given only distilled water through intestinal fistula. On December 20 extremely weak and apathetic. No twitching but occasional convulsive stretching into a position of opisthotonus. Given 50 c. c. 2 M. NaCl intravenously. Much improved and lived for three days longer with gradual reproduction of the same condition.

1621	December					
	18	19	20	21	22	23
Electrical excitability	KC	0.1	0.1	0.1 ↓ 0.2	0.1	0.1
	KO	Neg. 5	1.6	2.2	5.0	2.4 4.4
	AC	1.0	0.4	0.4	1.6	0.8 0.8
	AO	1.0	1.2	1.0	1.0	1.2 1.6
Plasma chlorides	6.9	7.7	5.8	3.8	6.0	5.6 4.5 4.2
CO <sub>2</sub> combining power	....	43.4	41.4	49.3	64.5	61.2 61.7 50.7 74.7

1622. Pylorus obstructed December 18, 1916. Animal given only distilled water through the intestinal fistula. The dog lived five days during which the plasma chlorides became greatly diminished and the alkali reserve increased. An attempt to introduce  $\frac{N}{10}$  HCl in dilute solution ended fatally.

1622	December					
	18	19	20	21	22	23
Electrical excitability	KC	0.1	0.1	0.3	0.3	0.1 ↓ 0.3
	KO	Neg. 5	5.0	Neg. 5	Neg. 5	Neg. 5 Neg. 5 Neg. 5
	AC	1.0	1.2	1.5	1.6	1.0 1.6
	AO	2.4	1.6	2.6	2.8	2.0 2.8
Plasma chlorides	7.03	6.99	....	4.48	3.54	2.79
CO <sub>2</sub> combining power	32.1	35.7	53.2	71.1	78.0	78.4 67.3

1704. Pylorus obstructed January 20, 1917, and animal given only distilled water through the intestinal fistula. The electrical excitability rose and on January 22 the dog had a violent convulsion lasting one minute. An hour later was given 50 c. c. 2 M. NaCl intravenously. Electrical excitability remained high but the dog was quiet and fairly well. On January 26, 50 c. c. 2 M. NaCl were again given intravenously. The dog remained alive until January 29 and there was no further twitching.

1704	January										
	20	21	22	23	24	25	26	27	28	29	
	NaCl					NaCl					
Electrical excitability	KC.....	0.05	0.10	0.05	0.05	0.05	0.2	0.05	0.1	0.1.....	
	KO.....	1.6	Neg. 5	1.6	2.8	2.8	2.6	Neg. 5	Neg. 5	2.8.....	
	AC.....	0.5	1.0	0.4	0.8	0.8	0.6	1.2	0.8	0.5.....	
	AO.....	0.9	1.6	1.0	1.2	1.0	0.8	1.6	1.0	1.0.....	
Plasma chlorides .....	6.1	5.7	4.1	4.1	4.6	4.6	3.6	2.5	4.1	3.7.....	
CO <sub>2</sub> combining power .....	44.7	38.1	43.0	44.0	47.3	68.6	69.1	82.7	70.0	71.5	94. ....

1705. Pylorus obstructed January 21, 1917. Given only distilled water by intestinal fistula. No symptoms on January 22 and 23, but on the morning of January 24 the dog was found in convulsions or "tetany." This was slower and more deliberate, less clonic than parathyroid tetany. There were no fibrillary tremors of the tongue. The convulsions were severe, stretching the animal into opisthotonus with attempts at vomiting. They were rather more like the convulsions of ammonia poisoning than those of parathyroid tetany. On January 24, after the convolution had lasted four hours, the animal was given 50 c. c. 2 M. NaCl solution intravenously. The convulsions disappeared and the animal lived until January 27 without any further attack.

1705	January							
	21	22	23	24	25	26	27	
	NaCl							
Electrical excitability	KC.....	0.2	0.5	0.05	0.2	0.6	0.6	0.4
	KO.....	1.2	Neg. 5	1.0	1.4	Neg. 5	Neg. 5	3.8
	AC.....	2.2	1.0	2.6	1.6	1.0	1.0	0.5
	AO.....	2.0	5.6	2.2	3.2	4.0	2.0	1.2
Plasma chlorides .....	5.7	5.6	4.4	4.4	....	65.3	71.5	34.5
CO <sub>2</sub> combining power .....	53.7	43.	47.3	....	....	....	....	....

1707. Pylorus obstructed January 26, 1917. As usual, the stomach was washed out twice daily and found to contain 300-500 c. c. of fluid. No symptoms until January 29, when there were violent convulsions. The mouth was opened wide and there were retching and salivation. No convulsions on January 30, but the animal was very stuporous and appeared to be dying. Given intravenously 100 c. c. 2 M. NaCl. January 31, very apathetic. Given 300 c. c. 2 M. NaCl intravenously, seemed rather improved but died in the afternoon. This was of course an extreme dose of sodium chloride amounting to 41 grams. It raised the plasma chlorides above the normal figure but only when the dog was moribund.

1707	January							
	26	27	28	29	30	31		
	Con- vul- si- ons			NaCl	NaCl			
Electrical excitability	KC.....	0.4	0.4	0.1	0.1	0.2	0.2	0.6
	KO.....	Neg. 5	4.0					
	AC.....	1.2	2.0	1.0	0.8	1.2	1.2	1.4
	AO.....	2.0	3.8	2.4	2.4	2.3	3.0	1.4
Plasma chlorides .....	6.2	6.1	5.2	4.5	3.6	4.7	10.0	.....
CO <sub>2</sub> combining power .....	60.0	45.0	58.0	64.0	74.9	65.3	24.2	.....

1714. Pylorus obstructed March 6, 1917. Given only distilled water by intestinal fistula. No symptoms until March 9 when violent convulsions with much frothing at the mouth occurred. In this case practically no change in electrical excitability was observed, although characteristic alterations in the plasma chlorides and alkali were present.

1714	March				
	6	7	8	9	
Electrical excitability	KC.....	0.3	0.2	0.2	0.2
	KO.....	Neg. 5	Neg. 5	Neg. 5	Neg. 5
	AC.....	1.2	1.0	0.7	1.0
	AO.....	1.8	1.6	1.0	1.8
Plasma chlorides .....	7.4	5.4	5.0	4.1	.....
CO <sub>2</sub> combining power .....	46.0	48.0	60.0	72.0	.....

From these experiments it is seen that a peculiar condition accompanied by convulsions appears whenever the pylorus is obstructed so that the acid gastric juice is all removed and no chlorides are given in the food. It must be recognized that the condition is not the same as that produced by parathyroidectomy. The muscular rigidity with vibrating clonic twitchings and extreme tachypnoea are lacking. Instead the rather apathetic animal usually lies quiet until seized with a violent universal convolution which throws the body into extreme and rigid opisthotonus with attempts at vomiting and abundant salivation. After this is over he sinks into a kind of coma with slow, deep respirations. Rapid respirations of great volume often precede the onset of the convolution. The electrical excitability is heightened definitely and up to the time of the convulsions it increases but never to a point comparable with that seen in parathyroid tetany, and even during the most violent twitching, stiffness and clenching of the jaws the KO reaches only 1.8 or 1.6, whereas in parathyroid tetany it is not unusual to have it 0.6 or 0.4.

The rapid diminution in the plasma chlorides with the corresponding rise in the alkali reserve as measured by van Slyke's method was constant. We, therefore, thought that the condition might be relieved by the replacement of the chlorides, and as a matter of fact injections of sodium chloride into the blood stream when the symptoms were well developed regularly caused the disappearance of the convulsions and a general improvement in the condition, and lowered for a time the electrical excitability.

When a dog otherwise treated in the same way, that is by obstruction of the pylorus and washing out of the stomach, was given distilled water with the addition of 10 grams of sodium chloride daily, it lived for a week or more without symptoms, maintained a constant proportion of plasma chlorides and a constant alkaline reserve as measured by the carbon dioxide combining power. Moreover, the electrical excitability of the nerves remained normal.

1711. Pylorus obstructed February 22, 1917. Given distilled water with 10 grams NaCl through intestinal fistula. Remained quiet; no twitching or convulsions. Walked about apparently well until February 27 when it was found dead. The wound had been torn open and there was an acute pleuritis.

		February.					
1711		22	23	24	25	26	27
Electrical excitability	KC	0.2	0.2	0.1	0.4	0.8	....
	KO Neg.	5 Neg.	5 Neg.	5 Neg.	5 Neg.	5 Neg.	....
	AC	1.2	0.8	0.7	1.2	2.2	....
	AO	1.2	0.8	0.8	1.2	2.8	....
Plasma chlorides	.....	6.8	6.6	6.4	7.0	8.0	....
CO <sub>2</sub> combining power	.....	43.8	50.4	52.2	50.1	49.0	....

1712. Pylorus obstructed February 26. Given distilled water with sodium chloride as before. Remained well until March 2 when he was apathetic and there were attempts at vomiting. Died on March 4 without infection or other obvious cause of death.

		February				March			
1712		26	27	28	1	2	3	4	
Electrical excitability	KC	0.1	0.1	0.1	0.1	0.3	0.6	....	
	KO Neg.	5 Neg.	5 Neg.	5 Neg.	5 Neg.	5 Neg.	5 Neg.	....	
	AC	0.8	0.8	0.8	0.6	1.6	2.2	....	
	AO	1.2	1.6	2.2	1.8	2.6	Neg 5	....	
Plasma chlorides	....	6.7	7.0	7.0	7.5	8.2	8.2	8.3	
CO <sub>2</sub> combining power	....	35.0	49.0	46.2	49.2	30.9	42.8	35.0	

We had of course regarded the whole alteration as due to loss of hydrochloric acid with the result that an excess of base had been left in the circulating fluids, so that the natural experiment would be the replacement of the chlorine ion by the introduction of hydrochloric acid. This was done several times but without much success (1620, 1622, 1709 and others), whereas the introduction of sodium chloride has a life saving effect and the administration of sodium chloride continuously after the operation prevented the development of changes in the electrical excitability, disturbances of the alkali reserves or symptoms. The fate of the Na ion requires explanation since it appears that so long as the Cl ion is supplied there is no heightened alkali reserve.

The prompt effect of calcium salts in stopping parathyroid tetany led to their trial in some of these cases. The injection of calcium lactate, although it exerts a temporary effect in stopping the twitchings or modifying the convulsions, has no such controlling influence, as is seen in the tetany following parathyroidectomy after which an animal can be kept perfectly well for a long time by the proper administration of calcium.

We had started with the idea that the loss of chlorides might throw out of function soluble calcium in the plasma or even actually precipitate it and we made numerous analyses of the blood to determine the changes in the proportion of calcium. The analyses were made (not to show the absolute, but the relative, amount of calcium in the plasma) by dialyzing 10 c. c. of blood received in 1 c. c. of 15% sodium citrate solution for 24 hours at 4° C. in a fish bladder sac against 100 c. c. of a solution containing 0.8% of sodium chloride and 0.3% sodium citrate. The clear colorless dialysate was boiled, acidulated and precipitated with oxalate after the method of McCrudden.

Titration were made against  $\frac{N}{100}$  potassium permanganate. Controls were made by estimating the calcium in the residue

in the sac and by analyzing the dialysate after known amounts of calcium chloride had been added to the blood and they show that a proportional amount of calcium appears in the dialysate. All that we venture to say from these studies is that there appears to be no characteristic change in the proportion of calcium in the blood from the time before the operation until the death of the animal. (As for the method, although it is probably open to many objections, it has the advantage of eliminating many difficulties in the analysis of blood for calcium and of giving accurate proportional results, which was all we required.)

It is clear, however, that there is a distinct change in the acid base equilibrium in favor of the alkali reserve and it seemed possible that this might be reproduced temporarily by the injection of sodium carbonate or bicarbonate which was done with the following results:

1614. Blood studied before injection: From 4.20 p. m. to 5.10 p. m. a gradual injection was made of 2 M. Na<sub>2</sub>CO<sub>3</sub>, 100 c. c. in all being run into the vein. The electrical excitability became greatly heightened temporarily. No convulsions were produced and there were no further effects.

		December 21							
1614		4	4.20	4.40	5	5.20	5.40	6	6.20
Electrical excitability	KC	0.1	0.1	0.05	....	0.05	....	0.1	
	KO Neg.	5 Neg.	5 Neg.	5 Neg.	5 Neg.	1.8	....	Neg. 5	
	AC	0.6	0.6	0.6	....	0.4	....	0.6	
	AO	1.0	1.0	1.4	....	0.6	....	1.4	
Plasma chlorides	....	6.8	....	....	....	6.4	....	7.2	
CO <sub>2</sub> combining power	....	50.4	....	....	....	119.6	....	74.0	

1623. Blood studied before injection. From 4.50 to 5.15, 160 c. c. 2 M. Na<sub>2</sub>CO<sub>3</sub> run into the vein. No marked symptoms, recovery prompt.

		December 22							
1623		4.20	5.20	6.20	7.20	8.20	9.20	10.20	
Electrical excitability	Na <sub>2</sub> CO <sub>3</sub>	....	....	....	....	....	....	....	
	KC	0.2	0.1	0.1	....	....	....	0.1	
	KO Neg.	5	0.8	1.0	....	....	....	Neg. 5	
	AC	0.8	0.5	0.6	....	....	....	1.2	
CO <sub>2</sub> combining power	AO	1.4	0.2	0.4	....	....	....	1.2	
	....	47.0	138.6	....	....	....	....	....	

1624. After normal electric reactions had been determined the injection of 10% Na<sub>2</sub>CO<sub>3</sub> into a vein was begun at 4 p. m. and continued to 5 p. m., 240 c. c. being run in. The animal became stiff with twitching and fibrillation of the tongue. Electrical excitability much heightened. Recovery complete.

		January 6				
1624		3.30	4.00	4.30	5.00	5.30
Electrical excitability	Na <sub>2</sub> CO <sub>3</sub>	....	....	....	....	....
	KC	0.5	....	0.3	0.4	0.2
	KO Neg.	5	....	....	2.6	1.0
	AC	1.6	....	1.6	2.4	1.0
CO <sub>2</sub> combining power	AO	1.6	....	0.6	0.6	0.4
	....	....	....	....	....	....

1701. Injection of 2 M. Na<sub>2</sub>CO<sub>3</sub> begun at 3 and continued to 4.15 p. m. during which time 150 c. c. were run in. After this the

electrical reactions disappeared and no contraction could be elicited. At 3.45 dog became stiff and stretched out. At 4 p.m. a violent convulsion occurred with twitching of the whole body.

November 30

1701	2.30	2.45	3.00	3.15	3.30	3.45	4.00	4.15
	Na <sub>2</sub> CO <sub>3</sub>				Convulsions Na <sub>2</sub> CO <sub>3</sub>			
Electrical excitability	KC	0.1	0.2	0.1	0.5	0.5	Neg.	
	KO	Neg. 5	Neg. 5	Neg. 5	Neg. 5	Neg. 5	Neg. 5	
	AC	0.6	0.6	0.6	0.6	0.6	Neg.	
	AO	0.9	0.5	0.3	0.2	0.4	Neg.	

1702. Injection of 1 M. NaHCO<sub>3</sub> begun at 3.15 and continued until 4.30 p.m., when 250 c.c. had been run in. Vomiting at 3.50. Generalized twitchings at 4.10. Slight convolution at 4.30. Prolonged and continuous convulsions at 4.50, after which all electric responses failed. Died at 5.15.

December 1

1702	3	3.15	3.30	3.45	4	4.15	4.30	4.45	5	5.15
	NaHCO <sub>3</sub>									
Electrical excitability	KC	0.4	0.2	0.3	0.2	0.2	0.2	0.2	Neg.	Died
	KO	Neg. 5	Neg. 5	Neg. 6	Neg. 5	Neg. 5	Neg. 5	Neg. 5	Neg.	
	AC	1.4	1.5	1.5	0.9	1.0	0.8	1.6	Neg.	
	AO	2.8	1.7	1.0	0.8	1.0	0.7	0.7	Neg.	

1704. Three c.c. per kilo of 1 M. Na<sub>2</sub>CO<sub>3</sub> were injected intravenously every 15 minutes. Weight of animal 11.45 kilos. This was begun at 10 a.m. and continued till 12.15, at which time 340 c.c. had been injected. The dog died shortly afterward. (Observations made by the students in experimental pathology under Dr. Admont Clark.)

February 7

1704	10	10.15	10.30	10.45	11	11.15	11.30	11.45	12	12.15
	Na <sub>2</sub> CO <sub>3</sub>									
Electrical excitability	KC	0.3	0.6	0.5	0.5	0.6	0.5	0.4		
	KO	Neg. 5	Neg.							
	AC	1.2	2.0	2.0	2.0	2.2	1.6	1.0		
	AO	2.6	2.4	1.4	1.4	0.9	1.0	0.5		
CO <sub>2</sub> combining power	46.6	55.1	69.1	73.9	83.3	87.6	98.4	101.4	112.0	121.3
Alveolar CO <sub>2</sub> (Marriott)	34.	33.	38.	42.	40.	43.	43.	44.	45.	

From these experiments it seems that practically the same symptoms, twitching, convulsions, opisthotonos, etc., can be produced by excessive injections of sodium carbonate or bicarbonate solutions as by the removal of the chlorides. The preponderance of the alkali over the acids is on a higher plane since there has been no loss of acid, but the relations are similar. The alterations of the electrical excitability parallel with those of the alkali reserve are just the same in the two cases. In both the increase of excitability is moderate and rather irregular. Sometimes it seems not to occur, while in other cases it is very definite.

An explanation of such phenomena usually means an interpretation in terms of simpler phenomena. Here we find that convulsions and heightened electrical excitability of the nerve muscle apparatus coincide with an excess of alkali. The same results are produced by the withdrawal of acid which could possibly disturb the relations of sodium, potassium, magnesium and calcium in the body.

It is possible that the disturbed equilibrium of acids and bases in itself is the cause of the symptoms. It is well known that the buffer qualities of the blood are such as to prevent any change in the actual PH. value without extreme interference with the alkaline reserve. The addition of acids lessens the alkaline reserve, but until it is used up there is compensated acidosis. Similarly the increase in the alkali content of the blood must be resisted to maintain the normal hydrogen ion concentration until an excessive amount of alkali is added. (This is not by retention of CO<sub>2</sub> because the alveolar CO<sub>2</sub> is increased.) A great excess of alkali must ultimately produce a marked change in the PH. of the blood.

The papers of Wilson, Stearns and Janney dealing with the condition of alkalosis in tetany following parathyroidectomy state that it may develop, but later on is neutralized by the acid products formed by the muscular activities incident to tetany. This result was reached by the study of the values of the dissociation constant of oxyhemoglobin, the alveolar CO<sub>2</sub> pressure and the hydrogen ion concentration of the blood. McCann confirms this by observations on two cases made by Van Slyke's method. In his first case he administered magnesium sulphate and calcium chloride and there is no way of telling the relation of the changes in alkali reserve to these procedures or to the tetany. In the second case he also removed the stomach contents at intervals, which would have its own effect. None of these writers records the chemical changes in time relation to changes in electrical excitability which are so important in the diagnosis of the condition of tetany. We ourselves in a few observations have found no change in the alkali reserve in the direction of alkalosis during tetany of parathyroid origin.

1617. Parathyroidectomy December 9, 1917. Tetany beginning December 11. On December 12, the dog was found in violent tetany. Given bicarbonate intravenously which did not relieve the tetany but appeared to add its own influence. No heightening of alkali reserve during the parathyroid tetany.

1617	9	10	11	12	NaHCO <sub>3</sub>
Electrical excitability	KC	0.05	0.05	0.05	↓ 0.05
	KO	Neg. 5	1.0	0.6	0.6
	AC	0.3	0.2	0.3	0.4
	AO	0.8	0.8	0.4	0.4
Plasma chlorides	.....	6.9	6.8	6.78	6.38
CO <sub>2</sub> combining power	32.8	45.4	39.8	36.5	74.9

1705. Parathyroidectomy December 18, 1917. On December 19 the dog was well. On December 20 there was violent tetany and death at 3 p.m. There was no increase in the alkaline reserve.

1705	18	19	20	December
Electrical excitability	KC	0.1	0.2	0.05
	KO	Neg. 5	Neg. 5	1.4
	AC	1.2	1.0	0.4
	AO	1.8	1.2	1.0
Plasma chlorides	.....	.....	.....	.....
CO <sub>2</sub> combining power	61.7	60.7	40.5	40.5

## CONCLUSIONS

When the pylorus is obstructed and the gastric juice with its hydrochloric acid is constantly removed, there ensues a decrease in the chlorine of the plasma.

There is a consequent increase in the alkali reserve which becomes extreme.

The electrical excitability of the nerves is in general heightened and there are spontaneous twitchings and in most cases violent convulsions which lead to death.

All of this can be prevented by constantly furnishing a large

supply of chlorides. It is less easy to cure the condition by the administration of chlorides.

The convulsive movements are not exactly like the twichings of the tetany of parathyroidectomy in which we have found no heightened alkali reserve, but they can be produced by the injection of sodium carbonate or bicarbonate.

Since these convulsions can be stopped or prevented by sodium chloride, it remains a problem as to what becomes of the excessive base sodium and as to the specific need of the chlorine ion. Further experiments are contemplated to settle these points.

## ACUTE CHOLECYSTITIS IN CHILDREN AS A COMPLICATION OF TYPHOID FEVER

By MONT R. REID and J. C. MONTGOMERY

(From the Surgical and Pediatric Clinics of The Johns Hopkins Hospital)

Following the report by Gilbert and Girode in 1890 of the case of a patient with typhoid fever from whose gall-bladder a pure culture of the typhoid bacillus was obtained, it soon became common knowledge that the gall-bladder is quite constantly infected by the bacillus during the course of the disease and not infrequently for months or even years after recovery. Chiari, in 1894, in his routine autopsies on 22 cases of typhoid fever, recovered the typhoid bacillus from the gall-bladder in 19 cases. The experimental work of Blachstein and Welch and the routine bacteriological examinations at autopsies in Professor Welch's laboratory also afforded early proof that Gilbert and Girode's statement in regard to a single case of typhoid fever would probably be applicable to all cases during some stage of the disease. It is now a well-known fact that the gall-bladder is probably always infected during the course of the disease and that the typhoid bacillus plays an important rôle in the causation of gall-stones and of cholecystitis.

The cases of empyema of the gall-bladder or acute typhoidal cholecystitis, however, that require surgical treatment or cause death during the course of the disease are few in number. Keen, in his work on "The Surgical Complications and Sequels of Typhoid Fever," reports only 30 such cases. Since his work appeared in 1898 only a few other cases have been reported. The rarity of severe gall-bladder complications during the course of the disease is also illustrated by the report of Hölscher who made post-mortem examinations on 2000 cases of typhoid fever. Of these, five showed gross pathological changes in the gall-bladder but in only one was there a perforation. More recently A. W. Webb-Johnson, in his careful study of 2500 cases of the typhoid fevers observed during the first half of the world war, reports only one case of acute cholecystitis in which surgical measures were resorted to, although in 15 cases the symptoms and signs of acute cholecystitis were sufficiently definite to be recognized.

In children acute suppurative cholecystitis of any kind is rare. Altogether there are only about 20 reported cases.\*

The recent admission to this hospital of a child with a large typhoidal empyema of the gall-bladder gave to most of us our first opportunity of observing a case of this kind, and incited in the writers the desire to study our hospital records and the literature relating to this condition in children. We will give the story of this case first, although it appears as No. 17 in the tables. The other cases that we have been fortunate enough to find have not been tabulated by any author and therefore deserve to be given in abstract form in this paper. The cases occurring in the service of Professor Halsted and filed in the records of this hospital have not hitherto been reported.

CASE 17.—The Johns Hopkins Hospital. Surg. No. 47082. A white girl of eight years came into the Pediatric Service of Professor Howland on December 20, 1918. She was admitted because of great emaciation, pain in the abdomen and a large abdominal mass. These abdominal symptoms had begun about one week before her admission and apparently at the end of a long illness which began on October 15, 1918, with high fever, delirium, headache, anorexia and some diarrhea. This illness lasted for eight weeks and during this time the child was treated at her home. Shortly before the abdominal symptoms began, the mother thinks the child had become afebrile and had begun to have a voracious appetite.

On admission to the Pediatric Clinic the patient weighed 40½ pounds. Her temperature was 98.8° F., pulse 100, and respirations 22. She was very listless and showed an extreme grade of emaciation. There were some recent and some old furuncles about the neck and shoulders. Over the sacrum and spines of the scapulae the skin showed a little reddening and thinning—beginning bedsores.

Further interest in the physical examination was centered entirely in the abdomen. It was asymmetrically distended, the right half and flank bulging more than the left. The skin venules were quite prominent. Abdominal respiratory movements were free. No peristaltic waves could be noted. A huge mass (outlined in the

\* It is mainly from the writings of von Khautz, Wharton, Eisen-drath, Osler and Mason that we have obtained these figures. See bibliography.

drawing) could be felt, and easily seen. It extended down to the level of the anterior superior spines of the ilia. Laterally and upward it was continuous with the mass in the flank and with the liver dulness. The surface of the swelling was smooth. There was no spasm of the rectus muscle. The lower and inner edge of the tumor was rounded and readily definable. The liver edge could not be felt. To some of those who examined the child the

bladder was suggested but not held to be very likely on account of the huge size of the mass.

The patient was transferred to Dr. Halsted's service and was operated upon by Dr. Reid on December 23, 1918. The seat of the trouble was found to be in the gall-bladder which was distended with between 700 c.c. and a liter of pus. The first pus to be evacuated was thin and yellowish; later it became thick and creamy. The gall-bladder was removed. No stones were present. After a moderately stormy convalescence the patient left the hospital on February 3, 1919. She gained weight rapidly and by the last of March was a normal healthy child with a slight tendency to obesity.

When the cultures from the gall-bladder showed a pure strain of *B. typhosus*, the case became clear. Previously we had believed that the swelling in the abdomen had been the sole cause of the child's illness and that it probably had begun with high fever, delirium, headache and diarrhea on October 15, 1918. We now came to the conclusion that the empyema of the gall-bladder was certainly secondary to typhoid fever and had probably developed toward the end of the disease. One week after the operation a culture from the urine showed typhoid bacilli and there was certainly a typhoidal pyelitis which disappeared before she was discharged.

The gall-bladder showed a typical picture of an acute hemorrhagic cholecystitis with necrotic areas of varying size.

CASE 1.—Husson, 1835. A child of eight years died in the third week of typhoid fever. The cause of her death was peritonitis which had developed during the course of the disease. At autopsy a perforation of the gall-bladder with resulting peritonitis was found. No stones were present.

CASE 2.—Archambault, 1852. An infant developed peritonitis in the convalescent period of typhoid fever. The autopsy showed an ulcerative cholecystitis with a perforation of the gall-bladder. The common duct was obliterated. [The presence or absence of stones is not mentioned.]

CASE 3.—Barthes and Rilliet, 1853. A child of 12 years died in the fifth week of typhoid fever. Whether the cause of death was recognized as due to a complication is not stated. The autopsy revealed a rupture of the gall-bladder with a large abscess formation about it.

CASE 4.—Chédevergne, S., 1864. This patient, aged 15, died on the fifteenth day of an illness diagnosed as typhoid fever. At autopsy an ulcerative cholecystitis was found.

CASE 5.—Stedman, C. E., 1882. A girl, aged 13 years, died on the twenty-fourth day of the disease with symptoms of peritonitis. At autopsy an ulcerative cholecystitis with a perforation of the fundus of the gall-bladder that had given rise to a general peritonitis was found. In the intestine were typical lesions of typhoid fever. No gall-stones.

CASE 6.—Stedman, C. E., 1882. A girl, aged six years, died of typhoid fever on the twenty-eighth day of the disease. The complication was diagnosed as a general peritonitis which was found at autopsy to be due to an ulcerative cholecystitis with three perforations in the fundus of the gall-bladder. The patient was a sister of the other patient whose case (No. 5) was reported by the same author.

It is interesting to note that Stedman reports the case of a third member of the same family, aged 16, who also had acute cholecystitis, but who recovered.

CASE 7.—Bond, J. W., 1886. The patient, aged 10 years, died during the course of typhoid fever from complications which were diagnosed as pneumonia and meningitis. At autopsy there was also found an empyema of the gall-bladder.

CASE 8.—Chiari, H., 1893. In the sixth week of typhoid fever the patient, aged 12 years, died apparently from pneumonia. The post-mortem examination revealed, in addition to a bronchopneumonia, a general peritonitis which was due to a ruptured

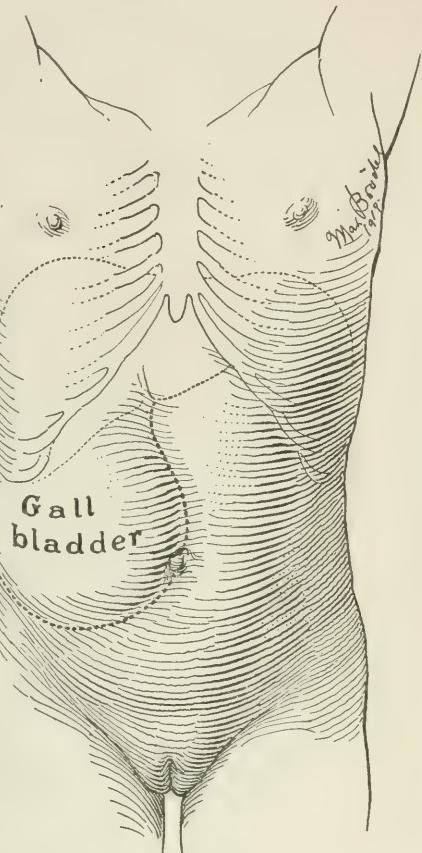


FIG. 1.—Outline of the gall-bladder. Case 17.

swelling appeared firm, elastic and possibly to be a solid tumor; to others it appeared fluctuant, particularly on bi-manual palpation through the right flank. The spleen and kidneys could not be palpated.

*Laboratory Findings.*—White blood count, 10,400. The vaginal smear showed no gonococci. The von Pirquet test was negative. The urine contained some albumin, and a few white blood cells. The kidneys secreted 65 per cent of phthalein in two hours. The X-Rays of the kidneys and chest showed practically nothing.

During three days' study on Dr. Howland's service the temperature varied between 99° and 104° F. No definite diagnosis was made. Retro-peritoneal sarcoma, sarcoma of the liver, cyst of the liver, abdominal abscess, appendix abscess, etc., were suggested by various men who saw her. An affection of the gall-

empyema of the gall-bladder. A culture from the abdomen showed *B. typhosus*.

CASE 9.—Alexieef, 1896. The patient, aged five years, developed during the third week of a well-marked case of typhoid fever the symptoms and signs of an acute cholecystitis. The gall-bladder was distended and a distinct fremitus was present over it. After this condition had persisted for about two days the child was seized with an agonizing pain, the abdomen became generally distended and the enlarged gall-bladder disappeared. These acute symptoms were probably due to a perforation of the gall-bladder, for a day or so later the operation revealed a peritonitis in the region of the gall-bladder due to a perforation of its wall. With

drainage the child made a good recovery. Very carefully made cultures showed *B. typhosus*.

CASE 10.—The Johns Hopkins Hospital. Surg. No. 12174. A white boy, aged 11 years, was admitted to the Medical Service in July, 1901, with a typical case of typhoid fever. On August 5, or about the beginning of the fourth week of the disease, he began to have severe abdominal pain. He had had several attacks during the night before his transference to the surgical clinic. When seen by Dr. Mitchell, who afterward performed the operation, the physical signs were typical of an acute cholecystitis with marked distention of the gall-bladder. There was a visible tumor just to the right of the umbilicus measuring about 5 cm. in diameter. Over this there was marked tenderness and muscle spasm. The

TABLE OF CASES OF TYPHOIDAL CHOLECYSTITIS IN CHILDREN

Case	Date	Age	Time	Diagnosis	Treatment	Result	Reported by
1	1835	8	Third week.	Typhoid fever.	No operation.	Death.	Husson: Eull. Soc. anat. de Par., 1835, 104.
2	1852	Infant.	Convalescing.	Typhoid fever. Peritonitis.	No operation.	Death.	Archambault: Bull. Soc. anat. de Par., 1852, 90.
3	1853	12	Fifth week.	Typhoid fever.	No operation.	Death.	Barthez et Rilliet: Traité des maladies des enfants, Paris, 1853, 2. éd., ii, 5; 701.
4	1864	15	Fifteenth day.	Typhoid fever.	No operation.	Death.	Chédevergne: De la fièvre typhoïde et de ses manifestations. Thèse de Paris, 1864, No. 173.
5	1882	13	Twenty-fourth day.	Typhoid fever. Peritonitis.	No operation.	Death.	Stedman: Med. and Surg. Rep. Bost. City Hosp., 1882, 3. s.
6	1882	6	Twenty-eighth day.	Typhoid fever. Peritonitis.	No operation.	Death.	Stedman: Med. and Surg. Rep. Bost. City Hosp., 1882, 3. s.
7	1886	10	Not determined.	Typhoid fever. Meningitis. Pneumonia.	No operation.	Death.	Bond: Jahrb. f. Kinderh., 1886, xxiv, 291.
8	1893	12	Sixth week.	Typhoid fever. Pneumonia.	No operation.	Death.	Chiari: Prag. med. Wehnschr., 1893, xviii, 261-263, Nr. 22.
9	1896	5	Third week.	Acute cholecystitis, typhoidal.	Drainage of peri-tonitis.	Well.	Alexieef: Jour. Dieteskaya Meditzina, 1896, No. 4; also in The surgical complications and sequels of typhoid fever (Keen), 1898, 268.
10	1901	11	Fourth week.	Acute cholecystitis, typhoidal.	Cholecystostomy.	Well.	Reported by the authors: Operator, Dr. J. F. Mitchell, Resident Surgeon, J. H. H., 1901.
11	1903	12	Eight months after recovery from typhoid fever.	Acute cholecystitis.	Cholecystostomy.	Well.	Reported by the authors: Operator, Dr. W. F. Sowers, Resident Surgeon, J. H. H., 1905.
12	1908	13	Convalescing.	Acute cholecystitis, typhoidal.	Cholecystostomy.	Well.	Reported by the authors: Operator, Dr. R. S. Miller, Resident Surgeon, J. H. H., 1908.
13	1908	12	Fifth week.	Typhoid fever. Intestinal perforation.	Exploratory laparotomy. Drainage of abdominal cavity.	Death.	Ashhurst: Am. J. M. Sc., Phila., 1908, cxxxv, 541.
14	1909	9	Second week.	Acute cholecystitis, typhoidal.	Cholecystostomy.	Well.	Reported by the authors: Operator, Dr. J. W. Churchman, Resident Surgeon, J. H. H., 1909.
15	1910	14	Third or fourth week.	Acute cholecystitis, typhoidal.	Cholecystostomy.	Well.	Prince: Surg., Gyn. and Obst., Chicago, 1910, xi, 416.
16	1911	15	Fifth week.	Typhoid perforation of intestine.	Cholecystostomy.	Well.	Reported by the authors: Operator, Dr. C. M. Remsen, Resident Surgeon, J. H. H., 1911.
17	1918	8	Convalescing.	Not made before the operation.	Cholecystectomy.	Well.	The authors' case.
18	1919	5	Fifth week.	Acute cholecystitis, typhoidal.	Cholecystostomy.	Well.	Deaver: Ann. Surg., Phila., 1919, lxix, 534-536.

general condition was fairly good. The leucocyte count was 10,000.

The operation was performed under cocaine anaesthesia. The gall-bladder was markedly distended and showed a definite area of beginning necrosis of its wall. The contents of the gall-bladder were a cloudy, serous-looking fluid which toward the end of the aspiration became slightly bile-stained. Under the microscope numerous clumps of bacilli were noted. In all about 300 c. c. of fluid were withdrawn. The gall-bladder was drained with rubber tubing. For a time bile was discharged freely, and when he left the hospital, six weeks after the operation, he still showed a persistent small biliary fistula. This probably closed soon after, for there is no record of the patient having had further trouble. Cultures from the gall-bladder showed *B. typhosus*. There were no stones present.

CASE 11.—The Johns Hopkins Hospital. Surg. No. 17406. A white girl, aged 12 years, developed symptoms of acute cholecystitis eight months after recovery from typhoid fever. She was admitted to Dr. Halsted's service February 21, 1905. The leucocyte count was 33,000. The temperature was 102° F. and the physical signs were typical of acute infection of the gall-bladder, associated with an indefinite mass. At the operation performed by Dr. Sowers, the gall-bladder was found to contain pus, ten small gall-stones, but no bile. Cultures were not made. The stones had probably been due primarily to the typhoid bacillus but on account of the acute nature of the condition and the high leucocytosis it is not unlikely that a secondary infection had been superimposed.

This case, strictly speaking, should not come in this series. We include it because of the age of the patient, and the relatively short period between the recovery from typhoid fever and the development of gall-stones.

CASE 12.—The Johns Hopkins Hospital. Surg. No. 22877. A negro girl, aged 13 years, was admitted to the medical service on July 22, 1908. The clinical picture and laboratory findings were typical of typhoid fever. On July 25, she had sharp abdominal pains accompanied by some tenderness below the umbilicus. These recurred on August 1 and at that time there was marked tenderness in the epigastric and right hypochondriac regions, associated with a rigidity of the right rectus muscle. There was no leucocytosis. On August 15, after having had a normal temperature for a few days, she had a relapse which was accompanied by sharp abdominal pains and a temperature of 103° F. On September 4 there was marked tenderness over the gall-bladder region, pain in the right flank and rigidity of the right rectus muscle. Under ether the gall-bladder was easily felt. At the operation (by Dr. R. S. Miller) it was found to be markedly distended with a watery purulent fluid. There were no stones. The gall-bladder was drained and the child made an uneventful recovery, leaving the hospital on September 26, 1908. A culture made from the pus of the gall-bladder showed *B. typhosus*.

CASE 13.—Ashhurst, A. P. C., 1908. A boy, aged 12 years, developed on the 32d day of typhoid fever, without previous symptoms, a very severe abdominal pain followed soon by the physical signs of peritonitis. A diagnosis of intestinal perforation was made and an operation was performed by Dr. G. G. Davis about five hours after the onset of the symptoms. A general peritonitis associated with a considerable amount of bile-stained fluid was found. There was no intestinal perforation. The patient was so sick that the peritoneal cavity was drained without any further attempt to discover the cause of the peritonitis. Death occurred 20 hours after the operation, and the post-mortem examination revealed a perforated gall-bladder. [There is no mention of cul- tures or of stones.]

CASE 14.—The Johns Hopkins Hospital. Surg. No. 24693. A negro boy, aged nine years, toward the end of the second week of typhoid fever was operated upon September 20, 1909, by

Dr. J. W. Churchman. The symptoms calling for surgical intervention had begun on the same day when the patient cried out with sudden severe pain in the abdomen, this pain lasting only a few minutes and then recurring frequently. The upper right half of the abdomen was tense and definitely distended. The gall-bladder could be felt. A slight difference in the two sides of the abdomen had been noted for several days before these acute attacks of pain and it was thought that a distended gall-bladder could be made out. There was an increase in muscle rigidity and definite jaundice. On account of acute attacks of pain associated with increased abdominal tenderness and a slight rise in the leucocyte count to 10,000, he was transferred to the surgical clinic.

At the time of operation the gall-bladder was distended with bile which, except for its thick consistency, appeared to be normal. Drainage with a tube was employed. The patient improved rapidly after the operation and left the hospital 54 days later. The wound was entirely healed. [There is no report of cultures.]

CASE 15.—Prince, E. M., 1910. A girl, 14 years old, developed in the fourth week of typhoid fever the symptoms of an acute cholecystitis. She apparently had not had attacks of pain in the gall-bladder region previous to the day of operation when symptoms came on very rapidly. The leucocyte count was 21,000. Temperature 104° F. Pulse 130. The abdomen was very tender. There was marked spasm of the upper right rectus muscle.

At operation, a much thickened and inflamed gall-bladder was found. The contents were "clotted bile." A cholecystostomy was performed. For three days no bile was discharged but after that it flowed freely. A culture of the contents showed a "motile bacillus." Convalescence was complicated by an otitis media.

CASE 16.—The Johns Hopkins Hospital. Surg. No. 26530. A negro boy, aged 15 years, during the course of typhoid fever and in the fifth week of the disease, developed signs which suggested to Dr. Remsen, who operated upon him, the probability of a perforation of the intestine. At the time of the operation the peritoneal cavity was free. The appendix showed a mild grade of inflammation which was thought to be due to a typhoid infection and the gall-bladder was markedly distended. The appendix was removed and the gall-bladder, although it did not appear particularly abnormal, was drained on account of its distention. In the gall-bladder there was thick bile but no stones. The walls of the gall-bladder itself were not necrotic. The cultures showed *B. typhosus*. The patient made an uneventful recovery and left the hospital about eight weeks after the operation.

CASE 18.—Deaver, H. C., 1919. This patient, a girl of five years, was in the fifth or sixth week of typhoid fever and apparently convalescing satisfactorily when she was taken with acute abdominal pain. This was so severe and the symptoms of peritoneal irritation so pronounced that an operation was performed within two hours of the onset.

A markedly congested gall-bladder with a necrotic area in its fundus was found. No perforation had occurred. The contents were a sanguopurulent fluid, from which the typhoid bacillus was grown. The Widal test made with these contents was negative. After the drainage of the gall-bladder the patient made a satisfactory recovery.

#### DISCUSSION

Altogether we have collected 18 cases of typhoid fever in children under the age of 15 who either died from, or were operated upon for, complications arising in the gall-bladder. In Case 11 of this series the acute cholecystitis did not develop until eight months after recovery from the disease; in all the other cases the complications came on during the course of the disease. Eight patients died without the interference of a surgeon. All of these cases were reported prior to the year

1893. Since that time 10 cases which have been treated surgically have been reported. One of these patients died—a mortality of 10 per cent.

The records of the earliest cases are not supported by any bacteriological studies. In recent years cultures of the gall-bladder have usually been made at the time of operation. In this connection the leucocyte count is of interest. When the cultures have shown a pure culture of the typhoid bacillus the count has been relatively low, usually about 10,000. In Case 12, in which cultures were not made, there was a leucocyte count of 33,000 and in Case 15, which showed an organism not definitely identified, there was a count of 21,000.

Thomas, in 1907, collected from the literature 154 cases of typhoid fever complicated by cholecystitis. Perforation of the gall-bladder occurred in 39 of these. Twenty-eight of the patients were not operated upon and died; 11 were treated surgically with a mortality of 54.6 per cent. In 1908, Ashurst collected 21 cases of acute cholecystitis in which an operation was performed during the course of typhoid fever. Eight of the patients recovered. Price, in 1916, collected eight other operative cases and added one of his own, this bringing the total of operations up to 30 cases. In Price's nine collected cases there was only one death and this was due to intestinal perforation two weeks after the operation on the gall-bladder. In the surgical clinic of this hospital the results have been good. The six children treated surgically and reported in this paper have all recovered. The good results in recent years are due mainly to the fact that the operations have been performed before rupture of the gall-bladder and partly also to better surgical treatment.

Emphasis should be put upon the importance of differentiating between gall-bladder complications that do and those that do not require surgical treatment. Slight pain and tenderness in the region of the gall-bladder, associated with a slight degree of spasticity of the right rectus muscle, are not so very unusual during the course of typhoid fever. The vast majority of these patients get well. Operating on typhoid fever patients for minor symptoms of cholecystitis is probably only slightly less justifiable than operating upon all patients that have pain in order to prevent intestinal perforation. Nevertheless, the low operative mortality justifies operation when there is grave doubt as to the nature of the condition of the gall-bladder. Acute suppurative typhoidal cholecystitis should receive immediate surgical treatment, for in such cases rupture of the gall-bladder may occur, and thus lessen many times the chances

of recovery. We believe that the best treatment is cholecystectomy.

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# X-RAY STUDIES OF THE SEMINAL VESICLES AND VASA DEFERENTIA AFTER URETHROSCOPIC INJECTION OF THE EJACULATORY DUCTS WITH THORIUM

## A NEW DIAGNOSTIC METHOD

By HUGH H. YOUNG and CHARLES A. WATERS

(From The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital)

The vast canal system extending upward from the orifices of the ejaculatory ducts in the verumontanum presents a wide field for study hitherto neglected both in urology and roentgenology. Only during the past few years has proper attention been paid to the rôle of the seminal vesicles in the production of any one of the numerous types of arthritis, cardiac and gastro-intestinal disturbances and neuroses, and up to the present time the assistance to be derived from the X-ray has been practically disregarded.

Belfield, Mills, Thomas and Pancoast and Picker have published excellent roentgenograms showing the vesicles and vasa injected with opaque substances through a vasotomy.

In the present paper we desire to call attention to a method by which the vesicles can be injected through the catheterized ejaculatory ducts following endoscopy, and, further, to emphasize the fact that, so far as our experience goes, there is no harmful effect associated with this procedure, and lastly to show that by the injection of thorium it is possible to outline the vast canal system above the orifices of the ejaculatory ducts.

It is generally stated in most text-books that strictures of the ejaculatory ducts do not occur and, as far as we can find in the literature, Luys is the only one who has attempted to explore the interior of the ducts by "catheterism."

For the past four years one of us (Young) has been endeavoring by means of specially devised probes, filiforms, bougies of metal and whalebone, and with Geraghty's utricle syringe (Fig. 1) to explore and treat the interior of the ejaculatory ducts, the vasa deferentia and seminal vesicles and in these experiments it has been found that the ejaculatory ducts are easy to locate in most cases even when not visible. A special probe will usually pass upward for a distance of 2 to 4 cm. into the vas deferens. In this way many differences in caliber have been discovered and several cases of marked stricture of the ejaculatory ducts have been made out.

In these cases systematic dilatations, done at weekly or bi-weekly intervals, have sometimes brought about almost immediate relief of chronic pain and discomfort in that region. In another paper a description of these cases, the methods employed and the results obtained will be given in detail. In the course of this work we have been struck with the need of a method by which the condition of the canal system above the verumontanum can be graphically depicted without resorting to opening the vas deferens in the groin as has been done by Belfield, Thomas and Pancoast, Mills and others.

With the introduction of thorium in making roentgenograms, it occurred to us to use this agent for the purpose of getting the much desired pictures of the inferior of the vasa

deferentia and the seminal vesicles. By using Geraghty's utricle syringe, it has been found easy in most cases to inject 1 or 2 c. c. of thorium solution and to obtain excellent radiographs of the vasa deferentia out to the external rings (Figs. 2) as will be described later on.

By means of the Young urological X-ray table (Figs. 3, 4, 5, 6) it is possible to make stereoscopic X-ray plates on the urological table immediately after injecting the ejaculatory ducts as shown in the illustration.

The utricle syringe is so constructed that the slender tip, which is about 1.5 cm. long, enters the duct for that distance and is then arrested by the shoulder.

This distance is apparently sufficient to carry it always into the vas deferens, as our radiographs have never shown the seminal vesicles when this instrument was used. With a shorter cannula, injections pass into the seminal vesicles.

In the progress of our work, having found it desirable to inject both ejaculatory ducts simultaneously, we devised a special forked cannula, one branch being 3 mm. longer than the other (Fig. 1-B). With this arrangement of the terminal tubes it is easy to introduce the longer tube into one duct for a distance of about 3 mm. and then be free to catheterize the other duct with the shorter tube, after which the instrument is pushed home until arrested by the junction point of the two tubes against the anterior surface of the verumontanum. With this forked cannula we have found it possible to inject 3 c. c. of thorium solution at one time and to inject both seminal vesicles.

We have thus demonstrated that catheterization of the ejaculatory ducts and radiographic study of the canal system above may be carried out with ease and that it furnishes a ready and satisfactory method of determining the condition of these structures. The process is apparently without danger. In some 50 cases in which the instruments and thorium solution have been introduced for varying distances into the vasa deferentia and seminal vesicles, we have never encountered an epididymitis or any other deleterious sequela.

The development of this method has been the direct outcome of the combined X-ray and urological table (Young's) by means of which it is possible to take radiographs while the patient is in a position for cystoscopy without disturbing him. This table makes it possible to place the patient in the horizontal, vertical, inverted and any intermediate position and to take radiographs in any of these positions without disturbing the patient or the urologist (note different positions of table in Figs. 3, 4, 5, 6). The roentgenologist is able to change his



FIG. 3.—Table horizontal with tube and compression attachment in position.



FIG. 4.—Side view of table in upright position.



FIG. 5.—Rear view of table in upright position, showing plate carriage in position for exposure.

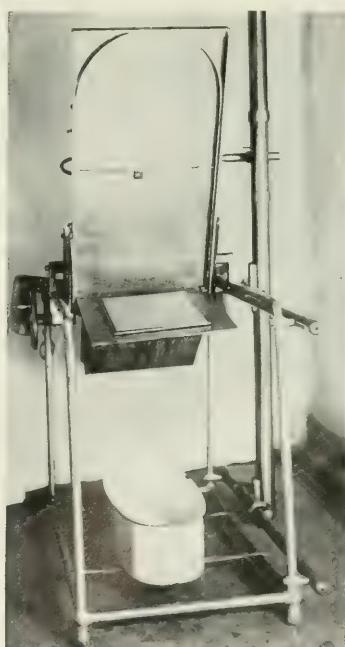


FIG. 6.—Rear view of table in upright position. Plate carriage and holder are lowered for reception of the plate.



FIG. 1.—Essential instrument used in the catheterization of the ejaculatory ducts. Note the specially devised forked cannula, (B), used in injecting both ducts at the same time. One arm of the fork is 3 mm. longer than the other. A.—Endoscope. B.—Double Forked Cannula. C.—Geraghty's Utricle Syringe.

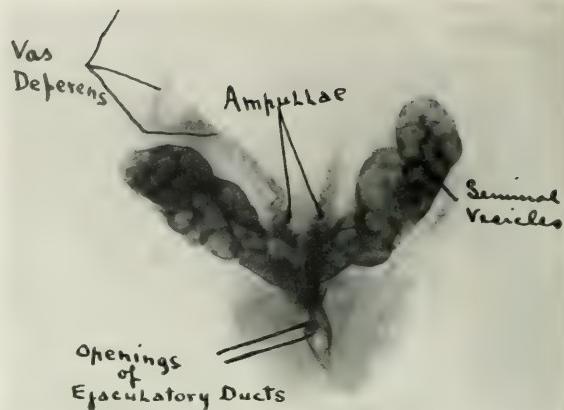


FIG. 7.—Showing the anatomical arrangement from an X-ray point of view.



FIG. 8.—Diseased vesicles and vas, showing marked irregularity and distortion.



FIG. 13.—Drawing made from stereoscopic plates showing both vasa injected.

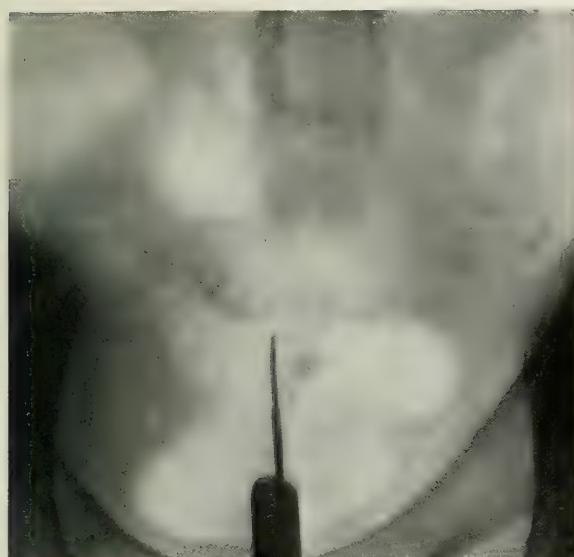


FIG. 2.—After the injection of the left side. Both vasa deferentia are now visible. The injections can be traced to the approximate location of the internal abdominal ring.



FIG. 9.—Shows the left seminal vesicle partially filled, the convolutions and sacculations appearing normal.



FIG. 10.—Injection with thorium showing the course, size and convolutions of the right vas deferens. The vesicles and left vas do not show in this plate. The syringe is seen in the lumen of the right ejaculatory duct. Left not yet injected.



FIG. 11.—Shows the forked syringe in the lumina of the ejaculatory ducts before injection was made.



FIG. 12.—Young's method of dilating ejaculatory ducts. Probe seen entering ejaculatory duct.





FIG. 1.—Vesicle projected through a prick-hole in the peritoneum.



FIG. 2.—A subsequent stage of the vesicle.



FIG. 3.—Its ultimate aspect.

plates for stereoscopy under the table with ease and dispatch, as shown in Figs. 5 and 6.

From an X-ray viewpoint, the anatomical structures of interest in the making of vesiculograms are (1) the verumontanum with the external openings of the ejaculatory ducts; (2) the ejaculatory ducts themselves; (3) the seminal vesicles; (4) the ampullæ of the vasa deferentia, and (5) the vasa deferentia above the ampullæ (Fig. 7).

The following vesiculograms have been prepared from autopsy specimens with a view of showing the variations existing in the anatomical structures. The specimens have been injected with thorium through the openings of the ejaculatory ducts. The anatomy is clearly shown; the lumina of the ejaculatory ducts are plainly reproduced; while the convolutions and windings of the seminal vesicles and the ampullæ of the vasa deferentia are clear and distinct. Variations in the vesicles and vasa deferentia have been observed. One typical plate is shown here (Fig. 8). The vesicles are greatly enlarged; their borders are irregular and indistinct and there is a loss of the normal sacculations and convolutions; both ampullæ are markedly enlarged and irregular. The vasa above the ampullæ are also seen to be dilated. The whole represents the pathological picture of an obstructive inflammatory process in the vesicles and ejaculatory ducts.

In Figs. 2 and 10 the syringe is inserted straight, first on the left side and then on the right. Only the vasa are seen. In Fig. 9, the syringe is inserted at an angle and only the vesicle

is seen. The explanation is that in the first instance the syringe passed by the opening of the vesicle and that, therefore, only the vas was injected, whereas, in the second instance, the syringe entered the vesicle and blocked the vas so that only the vesicle was injected.

Among the conditions for which this method seems applicable and helpful for diagnosis and treatment, the following may be mentioned:

1. To determine the patency of the ejaculatory duct or vas in cases of sterility when epididymo-vasotomy is contemplated.
2. To determine whether stricture of the ejaculatory duct, of the vas or of the outlet of the seminal vesicle is present.
3. To disclose the condition of the ampullæ of vasa or seminal vesicles in inflammatory or tuberculous conditions.
4. To show the condition of the seminal tract in studies to determine the cause of vague pain in the region of the prostate, vesicles or bladder. Other uses of this method will be forthcoming.

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## SELF-EVENTRATION OF A LARGE ABDOMINAL HYGROMA THROUGH A SCALPEL PRICK OF THE PERITONEUM

By W. S. HALSTED

On the 19th of May, 1893, a child two years old, was brought from the Out-Patient Department of The Johns Hopkins Hospital to the operating room with the request that she be tapped for ascites. On two or three occasions fluid had been withdrawn by the dispensary physicians from the distended abdomen, but on this morning repeated attempts to relieve the distension with the trochar and cannula had been unsuccessful, hardly a drop of fluid being obtained. The child's abdomen presented, as it seemed to us, the typical ascitic picture.

In making a short incision in the mid-line I accidentally pricked the peritoneum. Immediately there protruded through the prickhole a vesicle hardly larger than a mustard seed. The little bladder, slowly increasing in size (Figs. 1 and 2), soon covered the abdomen, and finally in saddlebag fashion fell over the child's flanks, a broad, flat isthmus of sac-contained fluid stretching across the now scaphoid belly from one great bag of water to the other, both of these resting on the bed-sheets (Fig. 3). The wall of this great cyst was of filmy thinness.

The mid-line incision was then lengthened and a search made for the pedicle about which several small cysts were found to be grouped. All of these seemed to have their origin in the great omentum—embryologically, in the posterior mesogas-

trium. An independent cyst, about as large as an orange, seemed to be contained between the layers of the duodenal mesentery, the continuation of the stomach's mesentery or posterior mesogastrum. This cyst was so adherent to the mesenteric vessels that we feared its removal might imperil the circulation of the bowel; hence we stitched its wall to the parietal peritoneum, and in a few days opened and drained it. The child made a prompt recovery.\*

Twenty-two years later, in 1915, after prolonged search, this patient was finally traced and persuaded to come to the hospital for examination. She was then 24 years of age, married and in good health. Her mother stated that she had suffered no ill effects from the operation. Examination of the abdomen revealed nothing abnormal except perhaps a little tenderness in the region of the appendix.

I have found no record of a case of abdominal hygroma observed so many years after operation for its removal.

The surgeon should bear in mind the possibility of lymphatic cyst whenever a child with distended abdomen comes under observation.

\* Full details of this case are recorded in the hospital history, Surg. No. 2245.

In April, 1916, an infant, aged seven weeks, was operated upon in extremity at The Johns Hopkins Hospital † for the relief of what was supposed to be intestinal obstruction. The

cause of the distension proved to be a lymphatic cyst, and the child promptly succumbed to the operation. It is conceivable that this infant might have been saved, had the correct diagnosis been made and the cyst evacuated or possibly eventrated through a small incision.

† Surg. No. 39451.

## THE UPTURNED EDGE OF THE LIVER OVER ACUTELY DISTENDED, EMPYEMATOUS GALL-BLADDERS

### A DIAGNOSTIC SIGN OF SOME VALUE

By W. S. HALSTED

A drawing made at the operating table about 20 years ago by the late August Horn depicts quite well the upturned edge of the liver over an acutely inflamed and distended gall-bladder (Fig. 1). This manifestation undoubtedly has been frequently observed by surgeons, and I direct attention to it merely on account of its occasional value as a confirmatory diagnostic sign. It may be much more pronounced than in the figured instance, and this ridge can be palpated if the abdominal wall is not too tense or abnormally thick. I cannot recall having noted this upturned or everted edge in the absence of signs of infection of the gall-bladder, but am not sure that it may not occur with hydrops vesicæ.

More than once this sign has enabled me in a debatable case to make the correct diagnosis. In one patient there was a non-resilient mass, larger perhaps than a man's fist, situated in the epigastrium and extending only slightly more to the right than to the left of the mid-abdominal line. Surmounting this mass was a linear, almost vertical ridge hardly 2 cm. to the right of the linea alba. The physicians of The Johns Hopkins Hospital who consulted me were inclined to believe that

we had a new growth under our fingers, and I was of the same opinion until on defining this ridge the correct interpretation occurred to me. At operation the mass proved to be made up of large intestine, duodenum, gall-bladder and a drawn out lobe of liver matted together and infiltrated with inflammatory exudate. The lobe of Riedel had been tugged to the right and so rotated that its upturned edge occupied rather a longitudinal than a transverse position.

In quite a number of cases in which the liver's edge over the gall-bladder, not upturned, was free and pliable, I have been able to feel it through the abdominal wall and to raise it on the back of a finger-nail insinuated between the gall-bladder and this hepatic lip.

I make it a point in every case of suspected enlargement of the gall-bladder to test for an overlying free border of the liver, upturned or not, and have much more frequently made it out in the flat than in the everted state.

There can hardly be anything new to experienced operators in what I have said, but for physicians the drawing may have interest.

## THE FATE OF BACTERIA INTRODUCED INTO THE UPPER AIR PASSAGES

### II. *B. COLI* AND *STAPHYLOCOCCUS ALBUS*

By ARTHUR L. BLOOMFIELD

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In studying the pathogenesis of infectious disease it is necessary to consider a set of factors quite apart from the inherent "virulence" or "invasive power" of the virus and the "resistance" of the tissues of the host in the stricter sense—namely, the conditions that determine the fate of the organism from the time when it reaches the body until it is eliminated or until actual invasion takes place followed, perhaps, by the production of disease. Such conditions are obviously complex and variable, and to a certain extent accidental. Thus, potentially pathogenic bacteria may reach the mouth only to be ejected or swallowed before disease can be initiated, or a small dose of organisms may perish under relatively unfavorable conditions where a part of a larger num-

ber might survive and invade the host; or anatomical variations in the polymorphous architecture of the body orifices may lead in one case to the harmless sidetracking of a germ which in another individual may perchance be deposited on a vulnerable point. On the other hand, there exist protective mechanisms more constant and orderly in their action which tend to destroy or to eliminate certain bacteria. The bactericidal effects of the mouth secretions may be mentioned as an example.

Despite the importance of exact information about the fate of pathogenic organisms during the period between their meeting with the host and their elimination or the inception of



FIG. 1.—Edge of Liver Everted by an Acutely Distended Gall-Bladder.



disease, we have at present only the limited and incomplete facts gleaned from epidemiological study. In the case of measles, for instance, it is probable that in the non-immune person inoculation is promptly and invariably followed by the production of disease—in other words, conditions are such that no effective opposition is offered to the invasion of the virus. In pneumonia, on the other hand, a different state of affairs exists. Although pneumococci are probably almost always transferred from the patient to the mouths of those in attendance, acquisition of the disease by direct contact is very unusual; and when a carrier state develops it is, as a rule, temporary.<sup>1</sup> It is clear, therefore, that a certain amount of opposition is offered to the free development and persistence of the pneumococcus in the mouth, and that this must be a factor in limiting the spread of the disease despite the potential virulence of the organisms and the susceptibility of the host. Similar reasoning may be applied to infections by other organisms such as the meningococcus, the streptococcus and others.

In a previous paper<sup>2</sup> it was suggested that information about the fate of bacteria in the upper respiratory tract might be obtained by actually placing the organisms on a definite site such as the tongue, tonsil, or nasal mucosa, and studying by repeated culturing their subsequent disposal. *Sarcina lutea*, which is non-parasitic and non-pathogenic for human beings, was employed. It was found that this organism swabbed in large amounts on the tongue or nasal septum or introduced into the tonsillar crypts could no longer be recovered after a brief interval, usually from one to two hours. This rapid disappearance seemed to be due to a direct destructive effect of the mouth secretions which kill the organism *in vitro* within one hour. The present paper deals with a similar study of bacteria which are usually non-pathogenic, but which are parasitic in human beings and may at times produce disease—*B. coli* and *Staph. albus*.

#### EXPERIMENTS WITH *B. COLI*

**Methods.**—The methods employed were essentially like those described in the previous work. The subjects were free from any marked abnormality of the upper respiratory passages and were not suffering from any acute disease. The bacteria were placed with a platinum loop on the selected site—the anterior half of the tongue, the mucosa of the nasal septum just posterior to the vestibule, or a tonsillar crypt. In the case of the last deep pocket-like crypts were chosen wherever possible so that the organisms could be deposited well within them. It required a considerable amount of practice to carry out this procedure successfully. The condition of the site of inoculation was always carefully noted and trauma was avoided. In no case was any local lesion or general reaction observed following inoculation. The patients were kept under direct observation for the first two hours of the experiment, and except in a few instances no food or fluid was taken until after the two-hour culture was made. The strain of *B. coli* used had been recently isolated from a stool and gave the typical reactions of this organism. Twenty-four hour growths on plain agar were used. The cultures were made on plain

agar to which from 5 to 10 per cent of sodium taurocholate was added. On this medium practically all of the usual throat flora were inhibited and the detection of *B. coli* was easy.

**Expt. I.**—*B. coli* was swabbed on the tongue and cultures were made from the tongue and the pharynx after 10 minutes, 2 hours, 24 hours, and 48 hours. The results are summarized in Table I.

**Summary.**—*B. coli* swabbed on the tongue was rapidly diffused over the whole mouth cavity. In three cases the organisms could no longer be recovered after 24 hours. In one instance a few colonies were recovered after 24 hours.

**Expt. II.**—*B. coli* was swabbed on the mucosa of the nasal septum and cultures were made from the nose and naso-pharynx after 10 minutes, 2 hours, 24 hours, and 48 hours. The results are summarized in Table II.

**Summary.**—*B. coli* swabbed on the nasal septum could not be recovered from the nose after 24 hours in 3 cases. In one case a single colony was recovered after this interval. The organisms were carried rapidly to the pharynx where they were recovered in variable numbers up to 24 hours.

**Expt. III.**—*B. coli* was introduced into tonsil crypts and cultures were made at various intervals for three or four days from the crypt and the pharynx. The results are summarized in Table III.

**Summary.**—*B. coli* introduced into tonsil crypts could be recovered after 24 hours in every case, and in one instance after as long as 48 hours. The organisms apparently were gradually discharged from the crypt over a period of from one to two days and no permanent carrier state was set up. Their persistence for a longer time in the tonsil crypts than in the pharynx (Expt. I) suggests that they are mechanically pocketed and prevented from being washed away. As long as the bacteria remained in the crypt a few could be recovered from the adjacent areas of the pharynx. In one instance (Mo) the control culture yielded four colonies of *B. coli*. This was the only control culture in the whole series in which *B. coli* was found. It probably represented a transient carrier state.

#### EXPERIMENTS WITH *STAPHYLOCOCCUS ALBUS*

**Methods.**—The same methods were employed as in the previous experiments, but the cultures were made on plain agar. The strain was obtained from the skin, and gave the typical cultural reactions.

**Expt. I.**—*Staph. albus* was swabbed on the tongue and cultures were made from the tongue and pharynx after various intervals. The results are summarized in Table IV.

**Summary.**—A large dose of *Staph. albus* swabbed on the tongue was rapidly spread about the mouth cavity. Practically all the organisms disappeared within 24 hours. After this interval a few colonies were recovered in one case, but not more than in the controls.

**Expt. II.**—*Staph. albus* was swabbed on the nasal septum and cultures were made from the nose and naso-pharynx after various intervals. The results are summarized in Table V.

**Summary.**—The majority of a large dose of organisms swabbed on the nasal septum disappeared in 24 hours. A few colonies could be recovered later but not more than were present in control cultures.

**Expt. III.**—*Staph. albus* was introduced into tonsil crypts and cultures were made from the crypt and pharynx at various intervals. The results are summarized in Table VI.

**Summary.**—The organisms disappeared rapidly. After 24 hours one colony was recovered from a crypt in one of three cases. There was no tendency toward the production of a carrier state.

TABLE I.—FATE OF *B. COLI* SWABBED ON TONGUE

Date	Name	Diagnosis	Age	Procedure	Number of Colonies of <i>B. coli</i> per Plate Recovered From Tongue and Pharynx								Control culture before inoculation	
					After 10 minutes		After 2 hours		After 24 hours		After 48 hours			
					Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx
Sept. 22.	Sp.	Tuberculous peritonitis.	16	½ slant <i>B. coli</i> swabbed on tongue.	** B. coli.	∞ B. coli.	∞ B. coli.	∞ B. coli.	No growth.	No growth.	No growth.	No growth.	No growth.	No growth.
Sept. 23.	Car.	Psychosis.	40	½ slant <i>B. coli</i> swabbed on tongue.	∞ B. coli.	∞ B. coli.	About 100 cols. B. coli.	About 200 cols. B. coli.	14 cols. B. coli.	B. coli.	No growth.	No growth.	A few cols. staphylococcus.	No growth.
Oct. 8.	Wa.	Myocardial insufficiency.	60	½ slant <i>B. coli</i> swabbed on tongue.	∞ B. coli.	About equal parts of B. coli and B. mucosus.	About equal parts of B. coli and B. mucosus.	Mostly B. mucosus.	No growth.	B. mucosus.	B. mucosus.	B. mucosus.	B. mucosus.	B. mucosus.
Oct. 9.	L.	Myocardial insufficiency.	55	½ slant <i>B. coli</i> swabbed on tongue.	∞ B. coli.	∞ B. coli.	∞ B. coli.	∞ B. coli.	No growth.	No growth.	No growth.	No growth.	No growth.	No growth.

TABLE II.—FATE OF *B. COLI* SWABBED ON NASAL MUCOSA

Date	Name	Diagnosis	Age	Procedure	Number of Colonies of <i>B. coli</i> per Plate Recovered From Nose and Nasopharynx								Control culture before inoculation	
					After 10 minutes		After 2 hours		After 24 hours		After 48 hours			
					Nose	Nasoph.	Nose	Nasoph.	Nose	Nasoph.	Nose	Nasoph.	Nose	Nasoph.
Sept. 23.	Lew.	Pleurisy.	30	½ slant <i>B. coli</i> swabbed on left nasal septum.	∞ B. coli.	4 cols. B. coli.	∞ B. coli.	No B. coli.	No B. coli.	2 cols. B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.
Sept. 23.	Lan.	Myocardial.	60	½ slant <i>B. coli</i> swabbed on left nasal septum.	∞ B. coli.	No B. coli.	∞ B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.
Oct. 8.	Lan.	Myocardial.	60	½ slant <i>B. coli</i> swabbed on left nasal septum.	∞ B. coli.	No B. coli.	1000 cols. B. coli.	1200 cols. B. coli.	1 col. B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.
Oct. 8.	Sp.	Tuberculous peritonitis.	20	½ slant <i>B. coli</i> swabbed on left nasal septum.	∞ B. coli.	No B. coli.	∞ B. coli.	A good many cols. B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.

TABLE III.—FATE OF *B. COLI* INTRODUCED INTO TONSILLAR CRYPTS

Date	Name	Diagnosis	Age	Procedure	Number of Colonies of <i>B. coli</i> per Plate Recovered From Tonsil Crypt and Pharynx								Control culture before inoculation	
					After 10 minutes		After 2 hours		After 24 hours		After 2 days		After 3 days	
					Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx
Sept. 23.	Lew.	Pleurisy.	30	One loop of <i>B. coli</i> placed in a tonsillar crypt.	∞ B. coli.	∞ B. coli.	8 cols. B. coli.	200 cols. B. coli.	10 cols. B. coli.	1 col. B. coli.	No B. coli.	No B. coli.	No B. coli.	No B. coli.
Oct. 7.	Mo.	Myocardial.	65	One loop of <i>B. coli</i> placed in a tonsillar crypt.	∞ B. coli.	6000 cols. B. coli.	∞ B. coli.	1000 cols. B. coli.	1000 cols. B. coli.	10 cols. B. coli.	1 col. B. coli.	No B. coli.	No B. coli.	4 cols. B. coli.
Oct. 7.	H.	Chronic endocarditis.	40	One loop of <i>B. coli</i> placed in a tonsillar crypt.	500 cols. B. coli.	No B. coli. plate overgrown by B. mucosus.	15 cols. B. coli.	No B. coli. plate overgrown by B. mucosus.	300 cols. B. coli.	No B. coli ; B. mucosus.	No B. coli.	No B. coli ; B. mucosus.	....	....

\* = innumerable

TABLE IV.—FATE OF STAPHYLOCOCCUS ALBUS SWABBED ON THE TONGUE

Date	Name	Diagnosis	Age	Procedure	Number of Colonies of Staphylococcus albus per Plate Recovered From Tongue and Pharynx										Control culture before inoculation				
					After 10 minutes			After 2 hours			After 24 hours		After 48 hours		After 72 hours		After 4 days		
					Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	Tongue	Pharynx	
Oct. 14.	Fa.	Tubes.	45	1 slant of Staph. albus swabbed on tongue.	∞ Almost pure.	∞ Almost pure.	∞ Almost pure.	∞ Almost pure.	About 50 cols. Staph. albus.	About 50 cols. Staph. albus.	2 cols. Staph. albus.	About 10 cols. Staph. albus.	0	0	0	0	0	About 10 cols. Staph. albus.	
Oct. 14.	Ba.	Cirrhosis of liver.	40	1 slant of Staph. albus swabbed on tongue.	∞ (pure).	∞ (pure).	∞ Almost pure.	∞ Almost pure.	10 cols. Staph. albus.	1 col. Staph. albus.	0	....	....	....	....	....	....	1 col. Staph. albus.	0
Oct. 14.	Ca.	Hypertension.	45	1 slant of Staph. albus swabbed on tongue.	∞ (pure).	∞ Almost pure.	∞ Almost pure.	∞ Almost pure.	20 cols. Staph. albus.	0 Staph. albus.	0 Staph. albus.	....	....	....	....	....	....	0	0

TABLE V.—FATE OF STAPHYLOCOCCUS ALBUS SWABBED ON NASAL MUCOSA

Date	Name	Diagnosis	Age	Procedure	Number of Colonies of Staphylococcus albus per Plate Recovered From Nose and Nasopharynx										Control culture before inoculation			
					After 10 minutes		After 2 hours		After 24 hours		After 2 days		After 3 days		After 4 days			
					Nose	Nasopharynx	Nose	Nasopharynx	Nose	Nasopharynx	Nose	Nasopharynx	Nose	Nasopharynx	Nose	Nasopharynx	Nose	Nasopharynx
Oct. 15.	Wa.	Myocardial disease.	60	1 slant of Staph. albus swabbed on left nasal septum.	∞ Almost pure.	0	Plate overgrown by spore bearer.	20 cols. Staph. albus.	Plate overgrown by spore bearer.	0	20 cols. Staph. albus.	20 cols. Staph. albus.	....	....	10 cols. Staph. albus.	0	About 100 cols. Staph. albus.	0
Oct. 15.	Sp.	Peritonitis (tuberculous).	20	1 slant of Staph. albus swabbed on left nasal septum.	∞ Almost pure.	0	∞ Almost pure.	20 cols. Staph. albus.	100 cols. Staph. albus.	10 cols. Staph. albus.	1 col. Staph. albus.	0	....	....	....	....	About 10 cols. Staph. albus.	0
Oct. 15.	Ma.	Convalescent pneumonia.	25	1 slant of Staph. albus swabbed on left nasal septum.	∞ Almost pure.	0	∞ Almost pure.	10 cols. Staph. albus.	10 cols. Staph. albus.	0	0	0	5 cols. Staph. albus.	0	....	....	A few cols. Staph. albus.	1 col. Staph. albus.

TABLE VI.—FATE OF STAPHYLOCOCCUS ALBUS INTRODUCED INTO TONSILLAR CRYPTS

Date	Name	Diagnosis	Age	Procedure	Number of Colonies of Staphylococcus albus per Plate Recovered From Tonsil Crypt and Pharynx										Control culture before inoculation			
					After 10 minutes			After 2 hours			After 24 hours		After 2 days		After 3 days		After 4 days	
					Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx	Crypt	Pharynx
Oct. 16.	Ha.	Chronic endocarditis.	40	One loop of Staph. albus placed in a tonsil crypt.	∞ Pure.	0	∞ Almost pure.	0	1 colony Staph. albus.	0	0	....	....	....	....	....	0	0
Oct. 14.	Falk.	Neurasthenia.	50	One loop of Staph. albus placed in a tonsil crypt.	∞ Pure.	A good many colonies Staph. albus.	∞ Pure.	A good many colonies Staph. albus.	0	1 colony Staph. albus.	0	A good many colonies Staph. albus.	....	....	....	....	0	A good many colonies Staph. albus.
Oct. 14.	Ba.	Myocardial insufficiency.	30	One loop of Staph. albus placed in a tonsil crypt.	∞ Pure.	Mixed plate.	∞ Pure.	Many colonies Staphylococcus albus.	100 colonies Staph. albus.	0	1 colony Staph. albus.	3 colonies Staph. albus.	....	....	....	....	0	0

**EXPLANATION OF THE DISAPPEARANCE OF *B. COLI* AND *STAPH. ALBUS***

As in the previous study with *sarcina lutea* an attempt was made to investigate certain factors which might be responsible for the disposal of the organisms, to wit, the reaction of the mouth secretions, mechanical removal by normal flushing processes in the mouth and nose, the destructive action of mouth secretions, and the possible antagonistic action of other bacteria present in the mouth.

*The Antagonistic Action of Mouth Bacteria.*—The question of the antagonistic action against invading organisms of bacteria present in the mouth opens a broad field of study about which we have at present very little exact information. Our impression is that the bacteria already present played no part in the disposal of *B. coli* and *Staph. albus*. This impression is based on the fact that these organisms thrive in mixed culture with the mouth bacteria in almost every case. In one individual (Ha), who was a carrier of *B. mucosus*, the plates were regularly overgrown by this organism and it may have played a part in preventing other bacteria from gaining a foothold.

*Reaction of Mouth Secretions.*—No practicable method was available for determining accurately the reaction of special regions of the mouth or nose. Furthermore, this did not seem advisable, inasmuch as the constant flux of secretions must lead to a continual alteration of the hydrogen-ion concentration. Systematic studies on this point now in progress have already shown that the pH of the mouth secretions may vary considerably from day to day in the same individual. A mixture of expectorated saliva and mouth secretions was therefore collected and its reaction was regarded as corresponding in general to that of the mouth surfaces. The pH of such secretions tested by the colorimetric indicator method has varied in about 50 observations made under various conditions from 6.2 to 7.4. Both *B. coli* and *Staph. albus* grew apparently with equal luxuriance on media whose reaction covered this range. Clark,<sup>2</sup> also, found the final hydrogen-ion concentration of cultures of *B. coli* on various media to be below pH 5.0. It seems unlikely, therefore, that the reaction of the mouth in itself explains the disappearance of these bacteria, although variations in pH may play a part in preventing or favoring rapid growth.

*The Bactericidal Effect of the Mouth Secretions.*—Equal amounts of a freshly expectorated mixture of saliva and mouth secretions were added to suspensions of a 24-hour growth of *B. coli* and *Staph. albus*. A standard loop of the mixture was plated at various intervals, and smears were made at the same time. An illustrative protocol of one of several experiments which gave essentially the same result follows (Table VII).

From this experiment it may be concluded that neither *B. coli* nor *Staph. albus* is killed by the mouth secretions in 24 hours. The experiment may be criticized in that the number of organisms used was very large and that a smaller number might have been inhibited or destroyed. It was desired, however, to determine only any gross destructive action which

the mouth secretions might exercise. The whole subject of the influence of salivas of various composition and reaction on the initiation of bacterial growth and the latent period requires further study.

*Mechanical Influences.*—After it had been determined that the mouth secretions exercised no destructive effect on *B. coli* or *Staph. albus*, other explanations for the disappearance of these bacteria were sought. The question immediately arose whether simple mechanical removal by the normal flushing of

TABLE VII.—EFFECT OF MOUTH SECRETIONS AND SALIVA ON *B. COLI* AND *STAPHYLOCOCCUS ALBUS*

B. COLI					
One standard loop from each tube plated at following intervals	Tube 1 0.2 c.c. mouth secretions pH 7.2	Tube 2 0.2 c.c. suspension <i>B. coli</i>	Tube 3 0.2 c.c. suspension <i>B. coli</i> + 0.2 c.c. mouth secretions	Tube 4 0.05 c.c. suspension <i>B. coli</i> + 0.2 c.c. mouth secretions	
Immediately.	No growth. (Bile agar).	<i>B. coli.</i>	<i>B. coli.</i>	<i>B. coli.</i>	
2 hours.	No growth. (Bile agar).	<i>B. coli.</i>	<i>B. coli.</i>	<i>B. coli.</i>	
24 hours.	No growth. (Bile agar).	<i>B. coli.</i>	<i>B. coli.</i>	<i>B. coli.</i>	

STAPH. ALBUS					
One standard loop from each tube plated at following intervals	Tube 1 0.2 c.c. mouth secretions pH 7.0	Tube 2 0.2 c.c. suspension <i>Staph. albus</i>	Tube 3 0.2 c.c. suspension <i>Staph. albus</i> + 0.2 c.c. mouth secretions	Tube 4 0.05 c.c. suspension <i>Staph. albus</i> + 0.2 c.c. mouth secretions	
Immediately.	Abundant colonies of various kinds.	<i>Staph. albus.</i>	<i>Staph. albus,</i> almost pure.	<i>Staph. albus,</i> almost pure.	
2 hours.	Abundant colonies of various kinds.	<i>Staph. albus.</i>	<i>Staph. albus,</i> almost pure.	<i>Staph. albus,</i> almost pure.	
24 hours.	Abundant colonies of various kinds.	<i>Staph. albus.</i>	<i>Staph. albus,</i> almost pure.	<i>Staph. albus,</i> almost pure.	

the mouth and nose by secretions or ingested fluid could account for their disappearance. It seemed desirable, therefore, to study the fate of inert particles placed in the mouth, nose and tonsil in a way similar to that employed in the case of the bacteria. For this purpose *Kieselguhr* and *rotten earth* were used. The former is a diatomaceous earth which is readily recognized under the microscope, the latter consists of insoluble crystals of characteristic form about the size of a red blood cell or larger, also easily recognizable. One or two loops of a thick saline paste of these substances was placed on the tongue, on the nasal septum, and in tonsil crypts. Scrapings were made at various intervals and examined microscopically. The

results of these experiments were uniform and striking. They may be summarized as follows:

TABLE VIII

## FATE OF INERT PARTICLES (KIESELGUHR AND ROTTEN EARTH) PLACED IN THE UPPER AIR PASSAGES.

Kieselguhr placed on the tongue could not be detected after 2 hours.

Rotten earth placed on the tongue could not be detected after 2 hours.

Kieselguhr placed on the nasal septum was detected after 2 hours but not after 24 hours.

Rotten earth placed on the nasal septum was detected after 2 hours but not after 24 hours.

Kieselguhr placed in a tonsil crypt was detected after 24 hours but not after 48 hours.

Rotten earth placed in a tonsil crypt was detected after 24 hours but not after 48 hours.

These experiments show that inert particles placed on the tongue, nasal septum, or in the tonsil crypts disappear at about the same rate of speed as *B. coli* or *Staph. albus*. The rapid disappearance from the nose at first glance seems especially remarkable, but it is in no way incompatible with what is known about the rate at which particles are transported by ciliated epithelium. Furthermore, as soon as the particles reach the inferior meatus the lachrymal secretion rapidly washes them to the posterior nares.

It appears, then, that while no direct destructive action is exercised upon *B. coli* or *Staph. albus* by the mouth secretions either *in vivo* or *in vitro*, conditions are such that the bacteria are removed by mechanical processes more rapidly than they multiply unless protected in some spot such as a tonsil crypt, where they remain relatively stagnant. There seems to be no tendency for them to take hold and grow diffusely in the mouth or nose.

## DISCUSSION

The present report represents part of a systematic study of the fate of bacteria introduced into the upper air passages. This study has so far revealed two distinct mechanisms for the disposal of such organisms. The first illustrated by sarcina lutea consists of a prompt and direct destruction of the bacteria by the mouth secretions. The second, illustrated by *B. coli* and *Staph. albus*, seems to apply to a group of organisms which have no tendency to grow diffusely or to localize in any part of the upper air passages, but which on the other hand are not directly destroyed by any bactericidal action. These bacteria seem to be removed by the normal mechanical flushing processes in the mouth and nose. It is possible that the study of other organisms will reveal still other mechanisms for removing invading bacteria.

The fate of *Staph. albus* brings up points of particular interest. This organism was selected for study because it may be recovered at almost any time in small numbers from the nose or mouth of normal individuals. We wished to determine

whether the introduction of a massive dose would lead to a permanent carrier state or whether the organisms would disappear rapidly. It was found that they disappear at about the same rate as *B. coli*, the number of bacteria recoverable promptly falling to the average or normal level. This observation seems to us to indicate that the few staphylococci ordinarily found in the mouth or nose are simply transients introduced from without the body, and that they are not actually growing or multiplying there as parasites. This presumption suggests further the general principle that some other members of the so-called mouth flora are organisms which are in transit into and out of the mouth and that they are not actual parasites. The whole subject of the constant variations of the mouth flora and their significance will be discussed at another time.

Observations such as those here reported raise the complex question of the relative favorableness and unfavorableness of the upper air passages as sites for bacterial growth. It should be emphasized that in dealing with environment we must consider every variation from conditions which are positively destructive to those which are simply unfavorable in the sense that a certain degree of resistance is offered to the initiation of optimal bacterial growth. An analysis of such conditions must include a consideration of certain qualities of the bacteria themselves such as the stage of growth, the size of the inoculum and the nature of the organism (source, virulence, etc.), as well as a consideration of the qualities of the medium, such as its reaction, certain chemical elements in its composition, the presence of other organisms, etc. These conditions are obviously endlessly complex and to a large extent defy exact analysis. It has seemed advisable in the present experiments, therefore, simply to gather the general facts about the disposal of organisms hoping later to deal more intelligently with particular details.

## CONCLUSIONS

1. *B. coli* and *Staph. albus* swabbed on the tongue or nasal septum usually disappeared within 24 hours.
2. *B. coli* and *Staph. albus* introduced into tonsil crypts could be recovered after somewhat longer intervals.
3. In no case was a permanent carrier state set up.
4. Inert particles disappeared at about the same rate of speed as the bacteria.
5. The organisms probably disappear because they are mechanically removed more rapidly than they multiply.
6. The disposal of *B. coli* and *Staph. albus* illustrates a mechanism radically different from that effective in removing sarcina lutea.

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# A CASE OF NON-PARASITIC HÆMATOCHYLURIA

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At the present time there are probably not more than a dozen cases of non-parasitic chyluria to be found in the literature. Several patients whose cases have been diagnosed as non-parasitic have lived in localities where filariasis is common and the diagnosis has rested upon the failure to demonstrate the embryos in the blood. Great caution should be used in diagnosing as non-parasitic the case of a patient who has dwelt in a filarial district, because the majority of chyluria cases result from infection by *filaria sanguinis hominis*. Filarial cases are known to clear up and the embryos disappear from the blood, so that we should reserve the term non-parasitic for the cases of those who have never been exposed to infection from *filaria*. Filariasis is an uncommon condition in the United States, although occasionally met with in Southern ports.

The case which I wish to report occurred in a young woman, 23 years of age, who has always lived in the mountains of Virginia:

Miss C. S., aged 23, from the mountains of Virginia, came in our clinic August 5, 1919, on account of the remarkable appearance of her urine and general weakness. The family history was essentially negative. The patient had never been strong and vigorous since an attack of chorea at nine years of age. Since that time she had always remained delicate, but had been able to assist in the household duties of her home. She had been rather nervous and for several years a facial tic had bothered her. At rather long intervals she had been subject to syncopal attacks which had caused her to lose consciousness upon several occasions. She usually had the attack after exercise and was always conscious of their approach. She had never bitten her tongue or had incontinence of urine during any of these attacks.

She had never had any pulmonary symptoms and her appetite had always been good. For a period of nine years, or since she was 14 years of age, she and her family had noticed an unusually milky appearance of her urine, which was always more marked in the morning. The urine at times had been perfectly clear, but for nine years, since the condition was first noticed, there had been no period of more than a few days that it had remained so. During the greater part of the time the patient had not been conscious of having any bladder or kidney trouble outside of the remarkable appearance of the urine. She had never been troubled with retention or incontinence, but she had frequently noticed that her stream would be interrupted by the passing of a clot. She could not recall ever having had attacks of pain that would suggest renal colic, and fever had never accompanied any of her bladder symptoms. She had noticed more frequent voiding when exercising but she had never been troubled with nycturia.

Her menstrual history was perfectly normal. The patient had weighed about 100 pounds for the past few years.

The following are the important physical findings:

The thyroid gland is slightly enlarged but there are no symptoms of thyroid intoxication.

Lungs.—Essentially normal.

Heart.—Mitral stenosis and insufficiency (compensated).

Abdomen.—No tenderness or rigidity. Liver and spleen not enlarged. No tenderness on deep pressure over the gall-bladder

region or McBurney's point. No abdominal masses made out. Kidneys in good position, not enlarged.

Pelvis.—Virginal outlet; rectal examination negative.

August 7: Cystoscopy by Dr. H. H. Hampton. No. 8 Kelly cystoscope passed.

Bladder normal in appearance. Ureteral orifices hard to find; normal in appearance. Right ureter catheterized with No. 8 renal wax-tipped catheter. No obstruction to catheter. A specimen from the right kidney urine, which is fairly clear, shows few red blood cells. Bladder urine, milky; contains red blood cells, leucocytes and oil droplets.

August 7: Functional test: Right kidney—collected through renal catheter; left kidney, from the bladder.

Amount of urine	Phenolsulphon-phthalein excreted
Right kidney 1 hour 15 c. c. ....	18%
Left kidney 1 hour 20 c. c. ....	15%
	<hr/> 33%

The urine from the right kidney was clear. The bladder urine was slightly milky.

August 11: Cystoscopy. A No. 8 Kelly cystoscope passed and a No. 8 bismuth renal wax-tipped catheter passed. Specimen from the kidney showed a clear urine with red blood cells. Culture taken. X-ray taken before and after a thorium injection shows a fairly large kidney shadow with the calices incompletely filled. Capacity normal, ureter not dilated, no stone or other shadows.

August 14: Cystoscopy. A No. 8.5 cystoscope passed after a bladder culture had been taken. Bladder urine milky, shows many red cells and a few leucocytes. The bladder wall was examined carefully for ulcers or diverticula, but none were found. The bladder was everywhere normal in appearance. The left ureter was catheterized but no urine was obtained. When fluid was injected it produced pain in the left flank. On palpation through the rectum, a thickened ureter could be felt on the left; the right ureter was not palpable. [This induration of the ureter might come from the passage of the catheter or tuberculosis.]

August 29: Cystoscopy. The bladder urine is milky in appearance, the cystoscopy having been done about two hours after lunch. The bladder is perfectly normal in appearance. There is a slight reddening of the ureteral orifices due to former catheterization, more marked upon the left side. Both ureters were catheterized with No. 8 wax-tipped renal catheters. Specimens of urine from both sides contained red cells and a few leucocytes; neither specimen was milky. There were no fat globules. No bacteria in hanging drop. No ova seen. Culture taken.

The patient was returned to the ward and given a meal—the regular ward diet, a fair amount of butter and two glasses of milk. Urine collected separately from both kidneys every hour for four hours showed the following:

First hour: Right kidney, very milky, but less so every hour until almost clear the last hour. None of the left kidney specimens was milky, but all contained traces of blood.

September 2: Cystoscopy. A No. 8 Kelly cystoscope passed. Bladder normal in appearance. A No. 8 bismuth catheter passed two-thirds of the way up to the right kidney. Culture taken. Pelvis capacity about 15 c. c. An X-ray taken before and after injection. Good picture obtained showed slightly dilated pelvis. Large kidney shadow. Ureter not dilated. Very small tortuous

linear shadows leading off from tip of calices into renal cortex. These shadows were rather indistinct and could be seen only in the negative.

Altogether the patient was subjected to five cystoscopic examinations within a period of four weeks. Cultures were taken from the kidneys and bladder at each sitting and all were reported negative except one bladder culture which was evidently a contamination (*Staphylococcus albus*). The bladder and kidney specimens were carefully examined a dozen or more times for tubercle bacilli but none were ever found. The bladder was given a careful routine examination at each sitting before catheterization of the ureter and was always found normal in appearance. Nothing resembling the mouth of a sinus was seen. Milky urine was always obtained from the bladder and large quantities of water were necessary to free the bladder of oil, even when the urine from the kidney was clear. I might mention here that it is not uncommon to find oil droplets in the urine that has remained in the bladder a week or more, following previous treatment, so that milky urine from the bladder is not positive evidence that the ureter is excreting milky urine at that particular time. For this reason both ureters should be catheterized simultaneously in investigating chyluria cases.

Several differential blood counts were made, all of which showed a slight eosinophilia. Otherwise there was nothing remarkable. The red count and haemoglobin were higher than one would expect in a patient suffering from a constant loss of blood; the red count being 6,123,000 and the haemoglobin 90 per cent. The fresh blood and smears were repeatedly examined for filarial embryos, but none were ever found. Wassermann test negative.

*Blood Study.*—On admission R. B. C. 6,123,000. W. B. C. 9160. Hgb. 90 per cent.

Differential Count P. M. N.....	75%
P. M. B.....	0
P. M. E.....	6%
Lymph.....	14%
Trans.....	3%
Smudges .....	2%
100%	

The X-ray of the thorax showed nothing suggestive of pulmonary tuberculosis.

*Urine.*—The urine varied in character throughout the day, being most remarkable in appearance early in the morning, and almost normal at times during the day. The first specimen voided in the morning (when the patient was on a fat-containing diet) was always milky and, upon standing, a light red, jelly-like clot would form and float near the top of the vessel, a bloody sediment collecting on the bottom. Portions of the clot were examined repeatedly, but nothing but blood cells and fibrin were ever found. The urine did not have the normal urinous odor, especially when fresh, but had rather a fleshy smell. Freshly voided specimens were usually acid, but some of the early morning specimens were alkaline. All specimens contained red blood cells in abundance, many leucocytes and albumin. No sugar was ever found. No parasites or ova were ever seen. The specific gravity varied from 1006 to 1018, the early morning specimen usually showing the highest for the day. No casts were ever found, all the specimens examined contained red blood cells and leucocytes.

*Experiments With Diet.*—Simple experiments with the diet were made over a five-day period, the urine being collected in four-hour portions. These were examined separately chemically and microscopically. Upon the first day the patient was given ordinary ward diet, which contains a moderate amount of fat. All the four-hour specimens were milky except the midnight specimen, which was cloudy. All specimens contained red blood cells, leucocytes and albumin. There was never any sugar. Altogether

1565 c.c. were voided. After the individual tests had been made upon the four-hour specimens, the remaining urine was collected in a single bottle and a fat determination made upon an aliquot portion with the Babcock lipometer, such as is used in rapid milk analysis. This gave 1.4 per cent fat, or 21.9 grams for 24 hours. Upon the second day the same diet was used, but water was forced. The patient excreted 2505 c. c. of urine with a fat determination of 1.2 per cent for the 24 hours, which gave a loss of 30 grams of fat. Each of the four-hour specimens was milky. The specific gravity was highest in the early morning, being 1012; lowest at noon, 1005. All specimens showed red blood cells, leucocytes, albumin and fat droplets; no sugar.

On the third day the patient took water as desired, but no food. The 4 a.m., 8 a.m. and 12 noon specimens showed fat in decreasing amounts. The 4 p.m. and 8 p.m. and subsequent specimens were fat-free. The 24-hour urine amounted to 1240 c.c. with an average of 0.2 per cent fat or 2.4 grams. It is perfectly evident that, had an interval been allowed after food, before the starvation specimens were saved, there would have been no fat in the urine upon the starvation day. On the following, or fourth day, the patient was given a fat-free diet with water as desired. The total urine amounted to 1750 c.c. All specimens were fat-free, which is ample proof that the urine would have been fat-free under starvation had time been given for the lymph to free itself of fat.

Upon the fifth and last day, the patient was given a fat diet with water as desired. All the four-hour specimens were milky. They contained an average of 1.6 per cent and a total of 2290 c.c. of urine was excreted, representing 36.6 grams of fat, roughly, about 30 per cent of the fat ingested, the fat intake being about 100 grams.

These experiments with the diet were not intended for a study of the fat metabolism, but were designed to prove that our patient was suffering from a true chyluria. They are very instructive, however, and would have been more so if we had determined the fat intake accurately and made fat determinations upon each four-hour specimen.

A second experiment was tried to shed some light upon the effect of posture upon the fat content of the urine.

Upon two successive mornings she was requested to empty her bladder and was given two glasses of milk before breakfast. One morning she was kept in bed and the next morning she was allowed to walk around the ward. The urine was collected every half hour for two hours. Upon both mornings all four specimens were slightly milky—the urine excreted while the patient was in bed containing a greater amount of fat than the specimens voided while she was on her feet.

We were anxious to conduct other experiments upon our patient but she wanted to return home and, as there was nothing to be done for her in a therapeutic way, we did not feel justified in holding her longer.

The literature upon this subject is not very large, although it extends over a period of half a century. Carter,<sup>1</sup> in 1862, presented two very interesting cases; one in an adult Hindoo, who had lymph scrotum and chyluria; the other in a Parsee youth who had a mass in his groin with a discharging lymph sinus. These cases of lymph scrotum that occur frequently in filariasis and this case of lymph sinus in the groin show the mechanical nature of the condition. All of these cases demonstrate that the rupture in the lymphatic system is due to mechanical blockage whether it be associated with inflammation or not.

Waters,<sup>2</sup> in 1862, reported a case of chyluria from which he drew the following conclusion: "I have come to the conclu-

sion that the affection is one in which the main pathological feature is a reflex condition of the capillaries of the kidneys, that as a consequence of this condition, the albumin, the fibrin, the fat and the blood corpuscles are filtered from the blood vessels and make their appearance in the urine." In Waters's case the condition cleared up (as often happens with filarial patients); he felt that good results had been obtained from the administration of gallic acid by the mouth.

Lüdke<sup>8</sup> in 1908, collected 10 cases of non-parasitic chyluria from the literature and reported a case of his own, in a woman 46 years of age. Hemoglobin, 90%; R. B. C., 4,408,000; W. B. C., 12,800. Urine acid, seldom neutral. She excreted from 6 to 8 grams of fat to 1000 c. c. of urine, which is a slightly lower excretion than in our case. The fat disappeared from the urine on fasting. He felt that his case was due to a connection between the lymphatic system and bladder, which he attributes to a colon cystitis.

Magnus Levy,<sup>4</sup> in a splendid article (1908), reviews the literature and reports a case of chyluria associated with diabetes in a man 51 years old. The condition was of six years' duration and unilateral, the chylous urine coming from the right kidney. The percentage of fat in the urine varied from 0 to 1.8%—about the limits in our case.

D. W. Carter,<sup>5</sup> in 1916, made a study of the fat content of the urine in a case of chyluria probably of filarial origin. He made repeated examinations daily for over a month upon his case. With a diet of 66.39 grams of fat, there was an average daily output of 6.45 grams. The amount of fat in the urine did not increase in direct proportion to the amount of fat ingested.

Stuerz,<sup>6</sup> in 1903, reported a case of chyluria as due to the presence of *Eustrongylus Gigas* in the left kidney, but since the chyluria did not clear up after nephrectomy, it seems very doubtful whether the two conditions were in any way related.

After reviewing a number of these cases, one cannot help being impressed by the influence of posture upon this condition.

Hnatek<sup>7</sup> reported a case of bilateral chyluria in a patient 33 years of age, who put out twice as much fat in the urine when in bed as when up and about; and four times as much fat from the left kidney as from the right.

Charteris<sup>8</sup> reports a case in which the chyluria was practically controlled by posture. The patient was an Austrian, 59 years of age, who had visited Egypt, India and Brazil. So far as he knew, he had never been infected with filaria. His morning urine was always milky but cleared up completely whenever he was upon his feet. Chyluria could be produced at any time by drinking a glass of milk and reclining at an angle of more than 45 degrees. The chyluria was most pronounced when the patient lay flat upon his back. Charteris concluded that "the chyluria was due to some intermittent pressure upon the thoracic duct by some factor that only became operative when the patient assumed certain attitudes." The patient would not submit to cystoscopy.

In our own case the morning specimen always contained the greatest amount of fat, although our experiment to demonstrate the influence of posture was not very conclusive.

The great majority of chyluria cases are periodic, our case being a notable exception.

Salkowski,<sup>9</sup> in 1907, reported a case of chyluria in a young man, 17 years of age, in whom the right kidney was responsible for the condition. This patient would have periods of three or four months in which his urine would be entirely normal, after which his chyluria would return. This periodical clearing up of chyluria has often led clinicians to attribute cures to many bizarre methods of treatment.

Pathological reports upon chyluria cases have been few in number. Mackenzie,<sup>10</sup> in 1882, reported an interesting case of filarial origin that has been frequently referred to in the literature, and I take the liberty of reproducing notes from his paper.

A soldier, 26 years of age, who had lived in India for more than a year, developed a serious chyluria, with attacks of left renal colic. Filarial embryos were demonstrated in the blood and urine. The urine contained the greatest amount of fat at night, but when the hours in bed were reversed, the day urine contained the greater amount of fat. The presence of embryos in the blood was also reversed by keeping the patient in bed during the day and letting him up at night. The patient died and following is the necropsy note:

The thoracic duct commences in a dense mass of lymphatic tissue and glands, which extends from the bifurcation of the aorta below to the level of the aortic opening in the diaphragm above. Looked at from behind, this mass occupies the whole of the space between the kidneys and is continuous below with the chains of lymphatic tissue on the iliac arteries.

The mass consists very largely of the enormously dilated lymph sinuses which can here and there be inflated. The receptaculum chyli commences by two large lymph sinuses about the size of a pencil, one from each side of the aorta and is joined opposite the aortic opening of the diaphragm by a third large sinus about the same size. The duct now ascends sinuous and much pouched for 3 to 4 inches, varying in diameter from  $\frac{1}{8}$  to  $\frac{1}{2}$  inch, previous for the first one and a half inches above the aortic opening of the diaphragm, then filled with a loose clot for one and a half inches, after which it is lost in a tough thick mass (inflammatory?). The occluded point in the thoracic duct, when opened, was found to contain a very long twisted clot, tapering at the end. It is left *in situ*, to be shown, before being submitted to microscopical examination. About four inches above this point, when it can be traced, although still involved in dense tissue, it is now the size of a small crow's quill, impervious and bending to the left side behind the aorta. At its termination in the angle between the left subclavian and internal jugular veins, it passes through a mass of lymphatic tissue, is impervious and about the size of a goose quill. As stated, the iliac, the lumbar and the renal lymphatics are very much enlarged and the enlargement is specially marked in the left iliac and the left renal lymphatics. Scattered throughout the left renal lymphatics are numerous hard masses, some the size of a pea but mostly smaller. These masses manifestly occupy the lymphatic sinuses.

Mackenzie did not feel sure as to the point of communication between the lymphatic and urinary systems, but he thought that it most probably was in the varicose lymphatics of the left kidney.

Haselburg<sup>11</sup> described a case in which the autopsy revealed a fistulous sinus (which exuded lymph) between the bladder and a tumor that extended up to the region of the left kidney.

Manson<sup>11</sup> observed at autopsy that the thoracic duct was obstructed and he removed a thrombus from its lumen. The connecting fistula with the urinary tract could not be demonstrated, but he noticed dilated vessels in the cut sections of the kidneys that he took to be dilated lymphatics.

Low<sup>12</sup> in his case found a practically normal lymphatic system except dilated lymphatics of the kidney from which he removed a calcified filaria. Varicose lymphatics were found in the bladder wall, but no fistulous opening was demonstrated. Low felt that he was dealing with a lymphuria that came through both kidneys and bladder.

In all three of these autopsy cases there were varicose lymphatics of the kidneys; in two of them there were demonstrable obstructions in the thoracic duct. In the third case, although there was no demonstrable obstruction of the duct, dilated lymphatics in both kidneys and bladder were found. All the cases were of filarial origin.

The clinical pictures of chyluria cases are remarkably similar, whether they are of filarial origin or not, provided the patients are not suffering from an active infection. In none of the cases I have reviewed have the kidneys been reported as being markedly diseased. The patients, unless suffering from active filarial infection, are usually in fair health with very few symptoms referable to the urinary tract, except occasional discomfort from the passage of clots. In none of the cases in which the blood picture is given was there any marked secondary anæmia, although blood was usually present in the urine. Many of the patients are undernourished, but are able to live upon an ordinary diet.

The etiology of the filarial cases is understood, but in the non-parasitic it is obscure. The chyluria seems to be most severe when the patient is in bed, the early morning specimen showing the highest fat content. In all cases there is more or less blood in the urine.

Magnus Levy<sup>13</sup> and Brandenburg<sup>14</sup> report interesting cases of chyluria associated with glycosuria.

What then is the best explanation of this condition? I believe that practically all cases depend upon mechanical obstruction of the lymphatic system, the obstruction usually being in the thoracic duct or large lymphatic trunks. The same factors are probably responsible for lymph fistulas of the lower extremities and scrotum. In most chyluria cases the chyle is found to be coming from one or both kidneys.

The cases of Haselburg<sup>15</sup> and Lüdke<sup>16</sup> demonstrate the occurrence of this lymphatic leak in the bladder, but some other bladder cases, in which the diagnosis was based upon a single cystoscopic examination without catheterization of the ureter, will not bear close analysis. We should not accept a diagnosis of bladder fistula until the kidneys have been excluded by bilateral catheterization of the ureters, the patient being put to bed and given a fatty meal and the urine collected for four hours. The first time our patient was cystoscoped her right ureter was catheterized and normal looking urine (except for a few red blood cells which are not unusual in the majority of catheterizations) was obtained. The catheter was left in one hour for a functional test and the urine remained clear during

that period. It was very difficult to wash the bladder clean of fat and every cystoscopist knows how common it is to find small bladder diverticula that might be mistaken for fistulous openings.

One observer reports a case in which he bases his diagnosis upon a single bladder examination with a water cystoscope, neither ureter being catheterized. He could not see any cloudy urine being discharged into the bladder, but found a fistulous opening back of the trigone around which a scum had accumulated. The clouding around the cystoscope was so intense that he withdrew it and found some milky fluid similar to that which he had observed in the urine. The chance of error under such circumstances is so obvious as not to need discussion.

We may safely assume, then, that in most of these cases the lymphatic leak is in the kidney. The few autopsies available tend to support this statement, but the actual connection between the lymphatics and kidneys has not been identified in a single case, nor is it likely to be demonstrated until the lymphatics are injected before removal of the kidneys. I believe that the kidney lymphatics represent the point of lowest resistance in the lymphatic system and when the thoracic duct or large trunks leading from the kidneys are blocked, they rupture just as an esophageal varix does under portal obstruction, or as the cerebral arteries do in hypertension cases. This theory will explain the similarity of most chyluria cases and will also explain the fact that, as a rule, the kidney function is not interfered with. It seems evident that the deep lymphatics of the kidney are involved and that they rupture into the tubules or directly into the calices. If this fistulous connection between the systems were dependent upon inflammatory lesions of the kidney, we would probably meet with the condition oftener, and we would also find diseased kidneys more frequently associated with chyluria.

#### SUMMARY

In summing up our case, we find that we are dealing with a case of non-parasitic chyluria that has persisted over a period of nine years in a young woman whose health is below par. She has a mitral stenosis that has given symptoms at intervals, for more than 10 years. Her chief complaint has been general weakness with frequent syncope attacks. Just how much of her disability has depended upon one or other of these conditions, it is difficult to say. Apparently her kidney function is unimpaired. There is no evidence of renal or pulmonary tuberculosis. From our simple experiments and clinical data we may draw the following conclusions:

- (1) We are dealing with a case of non-parasitic chyluria.
- (2) The leak in the lymphatic system in our case is located in the right kidney.
- (3) Upon starvation or a fat-free diet, the urine becomes fat-free, blood cells and albumin persisting.
- (4) Posture influences but does not control the amount of lymph leakage in our case.
- (5) Increased water intake and urine output increases the "fat loss."

(6) The leakage of lymph in most chyluria cases is located in one or both kidneys and location of this connection in the ureter or bladder should be made with caution.

(7) The connection between the lymphatic and urinary systems, which is usually located in the kidneys, probably consists of ruptured varicose lymphatics belonging to the deep lymphatic system of the kidney.

(8) Lymph fistulae, wherever they occur, are generally associated with mechanical blockage of the large trunks or thoracic duct.

I wish to thank the head of our department, Dr. Thomas Cullen, for permission to publish this case. My thanks are also due to Dr. Greenwald who did most of the clinical work.

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## A MYOMA OF THE UTERUS SHOWING UNUSUAL DEGENERATIVE CHANGES

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Mrs. M. G., aged 43, a patient of Dr. Amelia V. Zimmerman, entered the Church Home and Infirmary, May 6, 1919, complaining of an abdominal tumor. The family as well as the past general history of the patient was entirely negative. The menstrual history was of some interest. The onset of the menses was at 16; the duration of the periods was from three to five days and the patient had always suffered with moderate degree of dysmenorrhoea. During the last 10 years this dysmenorrhoea had been constantly increasing until, at the time the patient entered the hospital, she was suffering with bearing down pains in her abdomen and pains in the legs for two weeks of every month. For six months previous to her admission there had been a moderate amount of yellowish vaginal discharge. There was no history of intermenstrual bleeding, or urinary symptoms, or of any loss of weight.

The general physical examination was entirely negative, the patient being a well-developed woman, with no complaints except those which were referable to her pelvic condition. On pelvic examination, the external genitalia were normal. There was no pus in the urethra, but there was a moderate amount of yellowish vaginal discharge. The outlet was marital, but not relaxed. The cervix was high in the vault, firm, pointed forward, slightly lacerated. The fundus was about twice the normal size, irregular in outline, tightly fixed in the pelvis. The adnexa could not be felt.

Pre-operative diagnosis: Myomata uteri.

On May 7, 1919, Dr. Thomas S. Cullen removed the uterus, the appendix and the right tube and ovary. Through a midline incision the pelvic organs were exposed. The uterus was found to be enlarged and to have undergone myomatous

changes. On the right a large cystic mass extended out into the broad ligament and arising from the posterior surface of the uterus and extending into the left side of the abdominal cavity there was a large myoma. The operation was rendered extremely difficult by the large size of this cyst in the right broad ligament, to which the tube and ovary on that side were densely bound by adhesions and also because the right tube and ovary were bound tightly to the pelvic wall. There was considerable danger of cutting the ureter because of the extreme distortion of the pelvic organs, but by first exposing the ureter and following its course to the bladder before removing the tumor Dr. Cullen overcame this danger. The patient made an uneventful recovery and was discharged from the hospital in excellent condition three weeks after the operation.

*Pathological Report.*—Specimen No. 24993. The specimen consists of the right tube and ovary and the uterus with a large cyst attached. The tube is 8 cm. long. There are many adhesions around the tube, but its lumen is patent. There are no pathological changes to be seen with the microscope. The ovary measures 4 x 2 x 1.5 cm. and contains a small haemorrhagic cyst. The microscopic picture shows a corpus luteum cyst but is otherwise negative. The uterus with the large cyst attached measures 9 x 14 x 6 cm. On opening up the uterine canal, the endometrium is seen to have a yellowish tint. Sections from several portions of the uterus show a general myomatous condition with considerable variation in the number of cells, but nowhere is there any sign of malignancy. The cyst extending out into the right broad ligament is multilocular, heart-shaped, has a bluish color and extends downward from the lower surface of the uterus. On the inner



FIG. 1.—*a* shows course of duct running from the lateral wall of vagina out to the broad ligament;  
*b* shows line where cyst was cut.

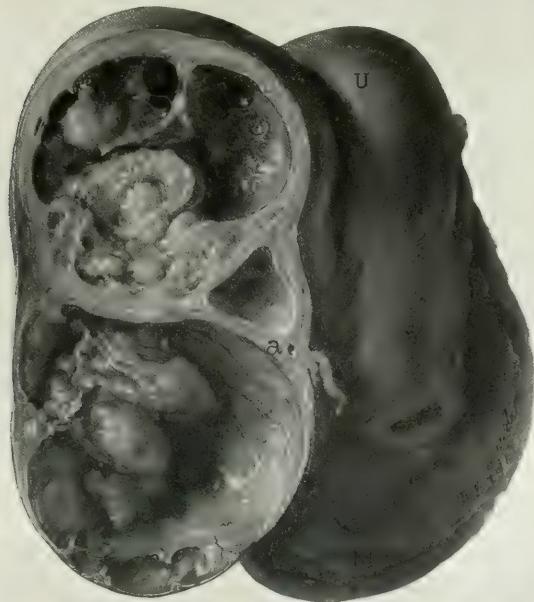


FIG. 2.—Cross-section of cyst at *b*. *a* shows cross-section of duct.  
*m* is myoma on left and posterior surface of uterus.





FIG. 3.—Low-power microphotograph: On right we see marked hyaline changes with the hyaline deposited especially around the blood vessels.

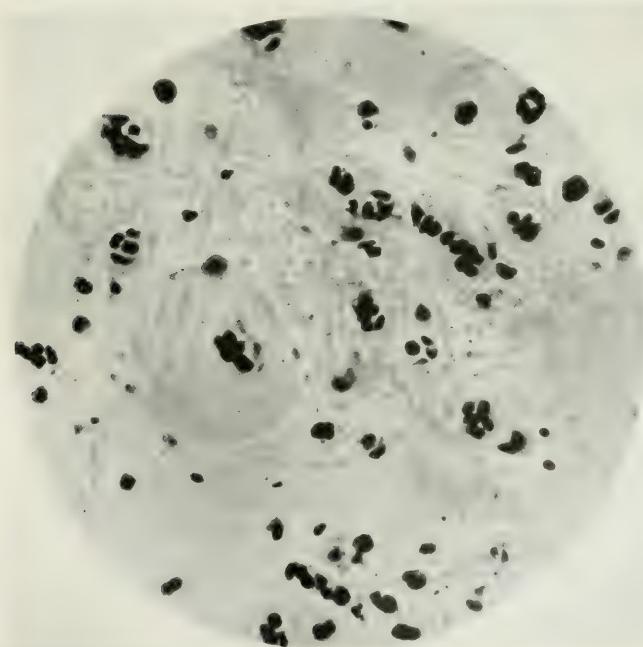


FIG. 4.—High-power microphotograph: The groupings of the nuclei in clefts resembling lacunæ is here shown.



and lower side of the cyst, about 2 cm. from the external os of the uterus, there is in the vagina an opening about 2 mm. in diameter. A small probe was introduced into this opening and a definite canal dissected out. This canal is well shown in Fig. 1, being marked by *a* and *a*.

Such a canal as here shown, extending upward from the lateral wall of the vagina along this cystic tumor, and then upward to the broad ligament, is in exactly the correct location for one of the rather rare embryonic remains of Gartner's duct. If this is the remains of Gartner's duct, the specimen is especially interesting, because we have here an opening of considerable diameter and a tube of uniform calibre, whereas in the majority of such reported cases the opening has been much smaller and the size of the lumen has varied greatly, being dilated in some portions, contracted in others. We know we are not dealing with a ureter here, because the course of the ureter was carefully traced at operation both before and after removal of the tumor and because sections of this duct show no transitional epithelium. Finally, we may have here an aberrant blood vessel anastomosing the ovarian and uterine arteries. Of course we know that ordinarily there are some anastomotic branches to these two systems, but to have a vessel of such caliber in such a location is certainly unusual. Cross-sections of the duct show a musculature resembling that found in an artery and no epithelial lining. Usually an epithelial

lining is found in a Gartner's duct, but in some cases this disappears.

The cyst was opened through the anterior wall at the point b shown in Fig. 1. A considerable amount of fluid poured out. The cyst is made up of several smaller cysts, each of which is filled with grumous material. For the most part the material is soft and fat-like in consistency, but on passing a knife over the cut surfaces, we get here and there a gritty sensation. In one of these smaller cysts there is a well-developed polyp. Sections from the cyst show that we are dealing with a myoma showing degenerative changes. First of all we have marked hyalinization with the hyaline deposited especially around the blood vessels. In numerous areas, as in the one shown in the right-hand side of the low-power microphotograph, only the shadows of smooth muscle can be made out, while in the high-power field we see only a few deeply stained nuclei and it is hard to be sure that we are not dealing with embryonic or indeed fully developed cartilage, for the heavily stained nuclei occupying clefts resembling lacunæ remind one strongly of cartilage cells. The clefts, however, we know are caused by the contraction of the smooth muscle fibers as they undergo degeneration, as is also the grouping of the nuclei.

I wish to extend my thanks to Dr. Thos. S. Cullen, through whose courtesy I am allowed to report this case, and to Mr. Max Brödel who made the drawings of the specimen.

## THE NEW WOMAN'S CLINIC AND THE CHANGE IN THE STATUS OF THE DEPARTMENTS OF GYNECOLOGY AND OBSTETRICS

On commemoration day, February 22, 1919, it was announced that an anonymous benefactor had expressed the intention of giving sufficient funds to erect upon the hospital grounds a building to serve as the woman's clinic for the medical school, and a few days later the General Education Board notified the university that beginning October 1, 1919, it was prepared to supplement the amount formerly expended by the hospital and medical school for the maintenance of the obstetrical department, so as to make it possible to place its teaching staff upon the so-called "full time" or university basis.

These generous benefactions have brought within sight the realization of long-felt hopes concerning that department, and at the beginning of the current academic year, Dr. Williams assumed his new duties, and henceforth will devote his entire time and energy to the hospital and medical school, although the department cannot be completely reorganized until the new clinic is ready for occupancy.

The donor has stipulated that "The clinic shall be devoted to the care and treatment of women before, during and after childbirth, and of women suffering from the various abnormalities of the generative organs, and shall afford provision for, and foster research into, any condition associated with the functioning of those organs."

It is hoped that the work of construction may be started early in the spring of 1920, and according to the plans now being perfected, the clinic will be an H-shaped structure occupying the sites of the present isolation, obstetrical and colored wards, and utilizing such portions of the existing buildings as may be practicable. It will consist of a basement, three full stories and a partial fourth story.

In the basement will be offices for the medical staff and for administrative purposes, teaching rooms and quarters for students on duty, a library, a museum and storage room. The first floor will be devoted to colored ward patients, both gynecological and obstetrical; the second floor to white ward patients; the third floor to private and semi-private obstetrical patients and to the research laboratories; while the fourth floor will be occupied by the gynecological and obstetrical operating rooms, the delivery rooms and the necessary space for supplies, preparation and administration. Gynecological private patients will be accommodated in the Marburg Building.

After the reorganization, which cannot be fully accomplished until the new building has been completed, the scope of the obstetrical department will be somewhat extended and will be under the direction of Dr. J. Whitridge Williams on the full-time basis.

As the result of the resignation of Dr. Howard A. Kelly, Dr. Thomas S. Cullen was made professor of clinical gynecology and placed in charge of this department, which in the future will be a sub-division of the department of general surgery.

The establishment of the woman's clinic will fill a long-felt need, and it is hoped that by placing obstetrics upon an adequately endowed full-time basis the patients will receive ideal care, more clinical material will be available for the instruc-

tion of students, and lastly, the opportunities for effective research will be greatly increased. It is also believed that in making gynecology a subdivision of general surgery a step has been taken which will prove of great benefit to students and particularly to internes and residents, in that they will have a training in the broader field of abdominal surgery rather than in a limited specialty embracing only a part of the surgery of the abdomen.

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## NOTES ON NEW BOOKS

*Nervous and Mental Disease Monograph, Series No. 30. The Internal Secretions and the Nervous System.* By Dr. M. FAIGNEL-LAVASTINE, of Paris. (New York and Washington: Nervous and Mental Disease Publishing Company, 1919.)

This monograph is a translation by Dr. F. T. Robeson, of New York, of an address written by the author for the Congress at Berne in 1914 and published in the *Revue de médecine*. It is 57 pages long and as one might expect, when such a large subject is thus briefly treated, it is only a tabulation and classification of possible symptoms. As such it will prove of value for quick refer-

ence to those who are already familiar with the subject. For those who are not, the discussion is too brief to afford a comprehensive grasp of the various syndromes mentioned.

F. A. E.

*Trench Fever.* By MAJ. W. BYAM, R. A. M. C. and Collaborators. (London: Henry Frowde; Hodder and Stoughton, 1919.)

This book represents the report of investigations carried out at Hampstead for the War Office Trench Fever Investigation Committee of the British Army. It contains chapters on the symp-

tomatology of the acute and chronic stages of trench fever, on prognosis and treatment, prophylaxis, immunity, pathology and the distribution of louse-borne diseases in the world. But the greater part of the book is an account of experiments on the mode of transmission of trench fever and the conclusions to be drawn. The results of these experiments, in entire agreement with those of the American Commission, leave no doubt in one's mind that trench fever is a louse-borne disease. This point having been established, the prophylactic indications are clear, and the chapter on this subject is well written and comprehensive. Probably more than any other chapter, that on the chronic stage of the disease will be of value to the profession in civilian work. Here it is pointed out that the disease may persist for many months and the symptoms of this chronic malady are discussed. Weakness, insomnia, cardiac instability, nervousness in a discharged soldier should suggest to his physician the possibility of a chronic stage of a previous acute trench fever.

There is a good index. The book is a satisfactory summary of the current knowledge of trench fever and should be useful as such. Its value would have been enhanced, however, by more care in recording references, for even short as the literature is on this subject, this very important factor in a book of reference has been largely neglected. At the end of the book there is an abstract of the report of the American Trench Fever Commission.

F. A. E.

*Psychoses of the War, Including Neurasthenia and Shell Shock.*  
By H. C. MARR, M.D., Lt.-Col. R. A. M. C. (Temp.) Fellow  
of the Royal Faculty of Physicians and Surgeons, Glasgow.  
(London: Henry Frowde; Hodder & Stoughton, 1919.)

According to the preface, this book is the result of observations on 18,000 men, "the number being almost equally divided between those suffering from neurasthenia and shell shock and those affected by obvious mental disorders." The introductory chapter, containing a review of brain anatomy and physiology based on unsubstantiated theories, assumes that the silent areas are the seat of the mind; then follows a section on the observation of mental phenomena which is limited to a description of facial expression in the psychotic and feeble-minded, pathological muscular movements, and the stigmata of degeneration! In the book there is no mention of the conflict of instincts and interests, no attempt to understand the individual from the standpoint of behavior. In fact, psychogenic factors are denied. The author claims that hereditary instability or inherent weakness of the nervous system in the majority of the cases and actual shock in those with negative histories account for the dissociation of the nervous mechanism. This is meant in a literal sense, since neurasthenia is defined as weakness of the neurone.

The second chapter covers all the war neuroses material, which the author discusses under the term hereditary and constitutional psychoses, dividing them into neurasthenia (shell shock) and neurasthenia of toxic origin which includes hysteria. The work ignores completely all the modern stimulating studies of the neuroses and the following quotation illustrates the type of sterile speculation which is employed throughout the book. "Simple neurasthenia acts by reducing the tone of the bodily system generally, so that when any sudden shock such as results from the explosion of a shell causes direct injury to the body, the abdominal sympathetic system is invariably affected, and the normal resistance of the intestinal tract to organisms is broken down, and their entrance, or the entrance of their products into the circulatory system, takes place." The hysterical features may persist as habits after the so-called neurasthenia has disappeared. The author acknowledges the value of suggestion, but lays little emphasis on it in the short section on treatment which consists mainly in general measures and tonics.

The remaining chapters resemble an old-fashion text-book of psychiatry, never getting away from the explanation by inherent

weakness of the neurones and auto-intoxication. The book adds nothing to the study of human behavior.

A. S.

*War Neuroses and Shell Shock.* By F. W. MOTT, M.D., Brevet Lt.-Col. R. A. M. C. (T.) (London: Henry Frowde; Hodder & Stoughton, 1919.)

Dr. Mott writes in an interesting manner of his experience with the war neuroses. He has not attempted to organize the material into chapters but has presented numerous short sketches without any definite arrangement. There follows in rapid succession 124 topics with no exhaustive discussion but with many brief quotations from authorities who have undertaken more special investigations. The range of the material is great and the book is therefore lacking in coherence. The author reviews the theory of shock, distinguishing between emotional and commotional shock (commotio cerebri). The mixed type predominates and in his opinion the psychogenic factor is by far the most important cause of the phenomena following the immediate results of the explosion. He gives some cases to illustrate the acute state of mental confusion, memory disturbances, various hysterical manifestations, etc. There is a tabulation of Wolfsohn's investigation showing that war neuroses were rarely associated with wounds, that the vast majority of cases had a neuropathic soil. A few pages scattered through the book are devoted to dreams, psychoanalysis and its technique. The various psychoses including those due to alcoholism and CO gas poisoning are discussed. The question of CO gas poisoning receives more detailed attention and is accompanied by plates showing the pathological changes in the nervous tissue. Brief mention is made of the various measures used in treatment of the war neuroses. The book instead of being useful as a systematic survey is so fragmentary that it gives one only a bewildering impression of the manifold problems that confronted the neuro-psychiatrist in the war.

A. S.

*Clinical Microscopy and Chemistry.* By T. A. McJUNKIN, M.D. Cloth, \$3.50. (Philadelphia and London: W. B. Saunders Co., 1919.)

The author has attempted in this volume to present the subject from the laboratory point of view, leaving the clinical interpretations for the instructor in Clinical Microscopy.

As a manual it serves a definite purpose though it may be said that there are a few things which might be added and some improved upon. For example, under agglutinating tests for blood to be used in transfusion, the method of using hollow ground slide preparations, which is probably the best method and in fact the one practically always used, is not mentioned.

It is true that in a brief discussion of various subjects not all the laboratory findings in various diseases can be mentioned; however, it would seem that an important finding, such as an increase in the percentage of eosinophiles in the blood of patients suffering from hookworm infection should be mentioned when outlining the clinical and laboratory findings in the disease.

The fact that an increase in the large mononuclears and transitory so often occurs in cases of Hodgkin's disease should be mentioned under the blood findings in this disease.

For ready reference for laboratory methods this book will be useful, although there seems to be little use for more books on this subject unless they are to include new methods.

H. M. C.

*Clinical Diagnosis: A Manual of Laboratory Methods.* By JAMES CAMPBELL TODD, M.D. Cloth, \$3.00. (Philadelphia and London: W. B. Saunders Company, 1918.)

As a manual of laboratory methods for the student or general practitioner this book apparently fulfills all requirements. The

descriptions are clear and concise. None of the commonly used laboratory methods have been omitted and some newer ones have been added. Among these are vital staining of red blood corpuscles, and the method of urobilin estimation in the stools as an aid in the diagnosis of pernicious anæmia.

There is a clear description of the method for matching bloods for transfusion purposes and also for determining easily the group to which an individual belongs. This latter method I have not found described in other text-books on clinical diagnosis.

The Wright and Kinnicutt method for counting blood platelets, which is perhaps the most simple and at the same time an accurate method, is here clearly described. Most of the books on clinical diagnosis mention this method but fail to describe it in detail, so that it becomes necessary to look up the original article to get the desired information.

The author has not intended his book for the trained laboratory worker but for the student and general practitioner, and for them it will prove very satisfactory.

H. M. C.

*Chronic Traumatic Osteomyelitis.* By J. RENFREW WHITE, M.D. (N.Z.), F.R.C.S. Cloth, \$3.00. (New York: Paul B. Hoeber, 1919.)

The great war has left many men maimed from all of the belligerent nations; among them none are to be pitied more than the sufferers from chronic traumatic osteomyelitis. The author of the book under review, in his introduction deprecates the fact that no treatment proved successful in preventing the dread sequelæ to compound fractures.

"In England," he says "we have as yet seen no results in fracture cases comparable to those of Leriche, no results comparable to those of Carrel. Shell and bomb fractures almost without exception have arrived in England cases of acute or chronic osteomyelitis; of the results of prophylaxis against this terrible disease little has so far been seen. Almost the only fractures that arrive 'simple' are those that have been 'simple' uninfected from the beginning—fractures, the result of rifle and machine-gun bullets and occasionally of shrapnel balls." He admits, however, that much prophylaxis was possible under ideal conditions, but he insists that such was not attained in the vast majority of cases, and he says that there are in England and throughout the world "tens of thousands suffering the discomforts and dangers inseparable from the constantly or intermittently discharging sinus, the result of a gunshot fracture."

With this condition in mind, the author urges every surgeon to acquaint himself with the pathology of this disease, and with the treatment by which most of these sufferers can be cured. The physiology of bone and the pathology of osteomyelitis are covered. The treatment outlined is orthodox and follows long accepted lines, still the insistence upon a thorough surgical procedure is stimulating. The frequent necessity of secondary operation following the primary major attempt is recognized. The post-operative case is detailed and preference is given to the Carrel-Dakin method, without however, advice as to the minutiae necessary for its successful use.

Although the style is involved, and renders the reading at times difficult, the book deals with a timely subject, covers it in a comprehensive way, and is well worth careful study.

A. S. I.

*Infection, Immunity and Specific Therapy.* By JOHN A. KOLMER, M.D. Second Edition. Cloth, \$7.00. (Philadelphia and London: W. B. Saunders Company, 1917.)

The same statement may be made of this second edition of Kolmer's "Infection, Immunity and Specific Therapy" that was made of the first, namely, "It is the most valuable book of its

kind in English Literature." Its value is now enhanced by the addition of a great deal of new and valuable material.

A brief mention of the new material with special reference to one or two subjects may suffice to give an idea of the increased value of the edition. The Schick test, which has a special field of usefulness in hospitals and institutions for the care of children is considered fully. The observation that the use of concentrated serum has lessened the incidence of serum sickness and facilitates the administration of large doses has been followed by a method, given in detail, for concentration of the serum. Very interesting are the studies by Dr. Schamberg, Dr. Raiziss and the author on the toxicity of Salvarsan.

Of equal interest is the new section on the treatment of infectious diseases, scarlet fever, poliomyelitis, pneumonia, etc., with specific serum from convalescent patients.

Among other new additions are: (1) The agglutination test in the differentiation of pneumococci; (2) the revised chapter on anaphylaxis and the special study of anaphylactic skin reaction; (3) a new method (Flexner) for the rapid production of anti-dysenteric serum by which effective serum for therapeutic purposes may be obtained in ten weeks.

The work may be recommended as a practical and thorough text-book on infection and immunity.

H. M. C.

*Clinical Diagnosis.* By CHARLES E. SIMON, B.A., M.D. Eighth Edition. Cloth.

The merits which belong to the former editions of Simon's "Clinical Diagnosis" are well known and the main interest in this volume is in the revised and new sections.

There is a new section on blood sugar with methods for its determination and one on complement fixation in the diagnosis of tuberculosis. The section on complement fixation in the diagnosis of cancer has been omitted. The author comments, "The hope that cancer might be diagnosed by this method has not been fulfilled."

The Lange colloidal gold reaction with a detailed description of the method, and with colored plates to show the reaction, has been added to this edition, as well as the new work on the determination of the existence of acidosis. The tests for blood matching have been included. There is also a detailed description of the ancestral types of various leukocytes with corresponding colored plates.

On the whole, despite the many new and changing methods in the field of clinical microscopy, the author has brought his book up to date. Methods in the old edition which have not proved valuable have been omitted and the newer ones have been added.

The colored plates are good and help to make the work a useful and valuable text-book.

H. M. C.

*Plastic Surgery, Its Principles and Practice.* By JOHN STAIGE DAVIS, PH.B., M.D., F.A.C.S. Instructor in Clinical Surgery, Johns Hopkins University; Assistant Visiting Surgeon, Johns Hopkins Hospital; Visiting Surgeon and Plastic Surgeon to the Union Protestant Infirmary, the Hospital for the Women of Maryland, and the Children's Hospital School, Baltimore, Md.; Fellow of the American Surgical Association, The Southern Surgical Association, etc. With 864 illustrations. Cloth, \$10.00. (Philadelphia: P. Blakiston's Son & Co., 1919.)

The book is divided into XXV chapters, the headings of which are as follows: I. Historical Review. II. General Considerations. III. Prostheses. IV. The Transplantation of Skin. V. The Transplantation of Other Tissues. VI. Pedunculated Flaps. VII. The Treatment of Wounds. VIII. Intractable Ulcers and Varicose Veins. IX. Scars and Keloids. X. Malformations. XI. Harelip and Cleft Palate. XII. Exstrophy of the Bladder. XIII. Epi-

spadias. XIV. Hypospadias. XV. Atresia of the Vagina. XVI. Plastic Surgery as Applied to the Various Regions. XVII. Surgery of the Eyelids. XVIII. Surgery of the Ear. XIX. Surgery of the External Nose. XX. Plastic Surgery of the Jaws, Lips and Cheeks. XXI. Surgery of the Lips. XXII. Surgery of the Cheeks. XXIII. Surgery of the Neck, Trunk and Extremities. XXIV. Surgery of the Extremities. XXV. Surgery of the Lower Extremity.

As he says in his preface, the author hopes that the book may show the general practitioner the possibilities of plastic surgery, start the student or beginner in this subject on the right track, and that in it even the more experienced surgeon may find methods with which he is unfamiliar, and which may be of use to him in dealing with plastic cases. He deplores the fact that hitherto plastic surgery has been limited to the region of the face, whereas it should include the entire surface of the body. Hence he has aimed to deal with the general principles of plastic surgery as applied to the whole body, and not the face alone.

Perhaps the key to the whole matter is to be found in the chapter on General Considerations. This deals in detail with incisions, plastic closure, needles and suture materials, methods of closing wounds without sutures, hemorrhage, drainage, dressings, massage and passive motion, etc. If the reader will study this chapter carefully before going on to those devoted to the regions, he will gain an adequate comprehension of the "little things which count for so much in the success or failure of this branch of surgery," and be better fitted to cope with the complications which arise after operative procedures.

The chapters on prosthesis, transplantation of skin, transplantation of other tissues, and pedunculated flaps, are complete in their scope and cover the ground thoroughly.

Those on the treatment of wounds, intractable ulcers and varicose veins, are carefully written, exhaustive and up-to-date. The author takes up the numerous methods of wound treatment and wound healing in a simple and clear manner, describing fully those methods which have proved to be of value, both before and during the recent great war.

The next seven chapters are devoted to malformations—congenital or acquired—such as scars and keloids, harelip and cleft palate, exstrophy of the bladder, epispadias, hypospadias, and atresia of the vagina. The last half of the book deals with plastic surgery as applied to the various regions, the different portions of the face, including the jaws, being taken up first, then the neck,

trunk, and extremities. The subjects are covered very fully; the old and new operations are discussed, the author giving his own experience and modifications of the usual procedures.

Many old and new operations are described for losses of substance, the repair of defects, the restoration of function, the relief of hideous and vicious contractures, and the reconstruction of the various parts of the face and body. The illustrations are numerous, the different steps in the operative work are fully described by line drawings, or actual photographs. In addition there are exhaustive bibliographies supplied for those who desire to devote more study to any particular branch of the subject.

The author is to be congratulated on having given us the only complete and up-to-date work on plastic surgery. It cannot fail to stimulate interest in this important branch of surgery and well merits to be widely read.

W. A. F., JR.

#### *Microbiology: A text-book of microorganisms, general and applied.*

Edited by CHARLES E. MARSHALL, Professor of Microbiology and Director of Graduate School, Massachusetts Agricultural College. Cloth, \$3.00. (*Philadelphia: P. Blakiston's Sons & Co., 1917.*)

This text-book, the work of numerous contributors, gives an excellent consideration of bacteriology as applied to agriculture and the special industries. There is good unity in the subject matter of the various chapters and there is little unnecessary repetition. The book is divided into three parts: The first treats of the morphology and culture; the second, of the physiology of microorganisms; the third occupies three-fourths of the book; it deals with "applied microbiology" and includes a great deal of information on the bacteriology of air, water, soil, dairy products, the microbiology of the special industries and the microbial diseases of plants, man and domestic animals. From the point of view of the non-medical student the treatment of immunity and the infectious diseases of man is quite adequate. Although the book has its most useful sphere among students of agriculture and domestic science it can be recommended to the medical student who has already acquired a knowledge of the microorganisms pathogenic for man as a means by which he may gain an insight into the development of that other branch of bacteriology to which the genius of Pasteur gave origin.

GREENSON.

## PUBLICATIONS

The following eight monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

Leukaemia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D. Price, \$2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICHT and T. WINGATE TODD. Price, \$2.00.

Other monographs will appear from time to time

# BULLETIN OF THE JOHNS HOPKINS HOSPITAL

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## EXPERIMENTAL PNEUMECTOMY

By GEORGE J. HEUER,  
*Associate Professor of Surgery, The Johns Hopkins University,*  
AND  
GEORGE R. DUNN,  
*Assistant Resident Surgeon, The Johns Hopkins Hospital, 1915-18*  
*(From The Hunterian Laboratory of Experimental Surgery)*

In the course of some experiments relating to thoracic surgery, carried on with many interruptions during the past six years by Drs. Henry Cave, E. Holman and ourselves, we have had occasion to remove the entire lung from 23 dogs. It seemed to us of interest to assemble the results obtained and to study them from various viewpoints: namely, (1) to discover the effects of total pneumectomy upon the pulse, blood pressure, and respiration; (2) to determine the results obtained in the treatment of the bronchial stump by various methods; (3) to observe the reaction on the part of the pleura upon the pneumectomized side—meaning by reaction the development or the absence of a pleural effusion; (4) to follow the fate of the intrapleural cavity resulting after removal of the lung and the methods of its obliteration; (5) to observe the reaction on the part of the remaining lung—by reaction meaning the development or absence of a simple enlargement associated with dilatation of the alveoli analogous to emphysema, or of a hypertrophy or of a hyperplasia; and (6) to estimate the probable duration of life in animals after a total pneumectomy. These various aspects of the subject are of predominant importance in lobectomy in man. They have been the subject of previous experimental work, but agreement in the results are often lacking. The results of our experiments should serve to clarify some of the mooted points.

The technic employed was quite uniformly as follows: (a) Intratracheal anesthesia with a positive pressure apparatus was always used. (b) In view of the infectious complications following previous experimental work, the skin was cleaned with the greatest care. After shaving and washing with soap and water, it was washed with alcohol and dried; then was washed with pure carbolic acid followed in a moment by alcohol. If the original scrubbing of the skin is not so vigorous as to cause multiple bleeding points, the skin does not suffer from this vigorous treatment and it was rare that even the slightest dermatitis followed it.<sup>1</sup> (c) An intercostal incision was made upon the left side, preferably in the fourth or fifth interspace. The chest was opened widely and the wound held apart with a rib spreader. The lung was drawn into the wound, the pulmonary arteries and veins at the hilus were individually isolated, doubly ligated with silk, and divided. The main bronchus or its main branches were isolated and stripped of all lung tissue. The lung was then removed, after the division of the naked bronchi. The divided bronchi were closed by the various methods to be subsequently described.

<sup>1</sup> The same technic has been used in human subjects; but here great care must be exercised not to allow the carbolic acid to run down over the skin; otherwise, an annoying dermatitis will result.

Before closure a culture was usually made from the mucous membrane just below the bifurcation of the trachea, in order to determine the bacterial flora in the upper air passages of the dog. The closed bronchial stump was dropped back into the pleural cavity, with no attempt to cover it with a fold of the pleura or pericardium. The wound was closed in layers with silk without drainage, the two ribs adjacent to the incision being brought together with encircling sutures. A simple collodion dressing was used to cover the skin incision. Before closure of the thoracic wall, the remaining lung was distended to its normal capacity.

*Summary of Results.*—In 23 dogs in which total pneumectomy was practised, there were 13 recoveries and 10 deaths. The fatalities occurred in from four days to two months after operation. Six of the deaths were due to an epidemic of distemper which swept through the kennels during the earlier period of our experimental work. The autopsy examinations in this group do not show a single instance of infection of the parietal wound or pleura or leakage from the bronchial stump.<sup>2</sup> One animal died of a simple pneumonia unassociated with other evidences of distemper. At autopsy there was no infection of the parietal wound or pleura or leakage from the bronchial stump. One animal died apparently from starvation, two months after operation. At autopsy there was a remarkable degree of emaciation, but no other assignable cause for death. There was no infection of the parietal wound or pleura or any leakage from the bronchial stump. Two animals died of acute pneumothorax, the result of leakage from the bronchial stump. In one of these the failure to secure an adequate closure of the bronchial stump was intentional. In the other a necrosis of the bronchial wall followed the application of an intentionally flattened (not rolled) metal band. These cases will be further discussed under the treatment of the bronchial stump.

The animals were kept under observation for intervals varying from several days to over one year. They were studied fluoroscopically from the day of operation onward, in order to determine (a) the presence of fluid in the pleural cavity from which the lung had been removed; (b) the position and movements of the diaphragm<sup>3</sup> upon the pneumectomized side as compared with the contralateral side; and (c) the mode of obliteration of the cavity left after the removal of the lung. When the animal was sacrificed, the thoracic organs were fixed *in situ* with the greatest possible care. The animals were anesthetized, placed in exactly the dorsal position; and, while being bled from the femoral artery, a 10 per cent formalin solution, introduced under low pressure into the vein, was carried throughout the circulation by cardiac action. At

<sup>2</sup> In every case which came to autopsy the tight closure of the bronchial stump was determined by immersing the stump in water and forcing air under high pressure into the trachea. The failure of air to escape from the bronchial stump was taken as an evidence of a satisfactory closure.

<sup>3</sup> In this part of the work, Heuer and Holman were associated and will subsequently publish in more detail the results of this phase of the work.

approximately the last respiratory effort a clamp was placed across the isolated trachea, and the body allowed to harden for several hours. The animals invariably died without a struggle. The illustrations in the paper are reproductions of photographs of dissections made upon animals fixed in this way.

*Technic of Lung Excision.*—Total lung excision is a very simple procedure in the dog. Through a properly placed intercostal incision the entire lung can readily be delivered, the larger vessels at the hilus isolated, doubly ligated and divided, and the main bronchus freed for a distance of several centimeters. The comparatively long bronchial stump lends itself readily to any one of a number of methods of closure, all of which if carefully done will ensure the air-tight closure and subsequent satisfactory healing of the stump. In the entire series there is not an instance of leakage from the bronchial stump when a serious effort had been made satisfactorily to close it. In one of the two instances in which leakage occurred, the simplest possible procedure was purposely used, the bronchus being simply ligated with a single fine silk (No. A) ligature. In the other instance a metal band was intentionally flattened instead of being rolled, and the probable necrosis of the bronchial wall at the proximal edge of the band was predicted. In dogs, then, it may be said that the satisfactory closure of the bronchial stump is possible. Infection, which played so large a rôle in the mortality in earlier experimental work,<sup>4</sup> has been eliminated as a factor in experimental lung

<sup>4</sup> Schmid, Hans: Experimentelle Studien über partielle Lungenresektion. Berl. klin. Wchnschr., 1881, XVIII, 757-759.

Lost 5 out of 8 dogs operated upon: 4 from sepsis, 1 from presumed acute carboxylic acid poisoning. He resected the apex of the lung only. His technic evidently was inadequate. His instruments and ligatures were apparently not boiled; simply placed in salicylic acid.

Gluck, T.: Experimenteller Beitrag zur Frage der Lungenextirpation. Berl. klin. Wchnschr., 1881, XVIII, 645-648.

Extirpated the lung in 6 dogs and 14 rabbits. A "few" of the rabbits developed pericarditis and septic pleurisy between the seventh and tenth days after operation. The operations were done under antisепtic precautions.

Block: Experimentelles zur Lungenresection. Deutsche med. Wchnschr., 1881, VII, 634.

Before undertaking the experiments the author studied the methods of Lister at the clinics of Küster and Volkmann. His first series of experiments consisted of the extirpation of the lung in 5 rabbits and 4 dogs. In no instance was he able to keep the animals alive longer than 14 days. The rabbits died for the most part immediately after operation; the dogs lived to the fourteenth day. Sepsis was the cause of death in the animals which did not die immediately. A month later he undertook a second series of experiments. All of the four animals submitted to operation died of a fibrinous hemorrhagic pleuritis.

Biondi, D.: Lungenextirpation bei experimentell lokalisierte Tuberkulose. Med. Jahrbücher, 1884, 207-216.

His experiments are complicated by the initial injection of tubercle bacilli into the lung, in the attempt to produce a localized pulmonary tuberculosis. About 25 or 35 days after the initial injection of tubercle bacilli the animals were operated upon and the lung resected. He made use of 10 rabbits, 6 cats and 5 dogs. About half the total number died of septic pleuritis or pericarditis after the initial injection. Four animals died immediately after the extirpation of the lung. Only 7 animals survived the extirpa-

excision. In the above series, with the exception of one of the cases cited above, in which leakage of the bronchial stump was followed by a pleural infection, there was no instance of infection of the parietal wall or pleura. That the infections in previous experimental work were due to faulty technic in the conduct of the operation exclusive of the treatment of the divided bronchus would seem evident from our earlier experiments, in which, after division of the main bronchus, a culture was made from the bronchial mucous membrane near the bifurcation of the trachea. These cultures were almost invariably sterile, a finding which in the absence of leakage from the stump would largely eliminate the bronchial mucous membrane as a factor in the causation of pleural infections. That the pleura is peculiarly susceptible to infection, as has been quite generally believed—and largely as result of the incidence of infection following experimental intrathoracic operations—would not seem to be borne out by some experiments that are not yet completed. The occurrence of pleural effusions following lung excision as a factor in the mortality—commented upon by a number of authors—will be discussed when we come to discuss the reaction of the pleura following pneumectomy. It may be stated here that our experiments would indicate that the occurrence of pleural effusions after excision of the lung is probably entirely the result of infection of the pleura and rightfully should play no rôle in the mortality. In the absence of complicating factors (distemper, etc.), and with an adequate technic and careful

tion of the lung. Although the author states that he used great care in his technic, 9 animals developed a septic pleuritis following the extirpation of the lung.

Murphy, J. B.: "Surgery of the lung," *J. Am. M. Ass.*, 1898, XXXI, 151, 208, 281, 341. Five of the nine animals operated upon died of sepsis.

Robinson, Samuel: *Ann. Surg.*, 1908, XLVII, 184.

In 30 thoracotomies upon dogs performed under positive pressure anesthesia (of which 12 were simple pleurotomies without interference with the lung, 15 with resection of a part of or an entire lobe, 1 with removal of two entire lobes, and 1 with removal of the entire lung) there were 5 deaths from sepsis, one case of sepsis being due to leakage from the bronchial stump, and four additional cases of infection (either localized empyema or parietal wound infection) the animals, however, recovering.

Halsted, W. S.: *Tr. Am. Surg. Ass.*, 1909, XXVII, 111.

In 21 consecutive thoracotomies there was only one primary infection of the thorax—a marked contrast to the hitherto reported results.

Meyer, Willy: *Zentralbl. f. Chir.*, 1909, XXXVI, 1713-1716. *Also: J. Am. M. Ass.*, 1909, LIII, 1978.

In 21 total extirpations there was one death due to sepsis and one due to leakage from the bronchial stump.

Robinson and Sauerbruch: *Deutsche Ztschr. f. Chir.*, 1909, CII, 542-560. *Also: Zentralbl. f. Chir.*, 1910, XXXVII, 391.

In 38 simple total extirpations of the lung under positive pressure (including those of Haecker) there were only four recoveries. In 18 there occurred a marked transudation into the pleural cavity upon the operated side (infection?) followed by death; five animals died from sepsis, 11 from leakage from the bronchial stump.

Kawamura, K.: *Deutsche Ztschr. f. Chir.*, 1914, CXXXI, 189-222.

Of 23 animals operated upon, 3 died of sepsis, 2 cases being secondary to leakage from the bronchial stump.

closure of the bronchial stump, the mortality in experimental pneumectomy in dogs—previously very high—may be reduced to a minimum.

*Pathological-physiology of the Circulation and Respiration During and After Total Lung Excision.*—In the course of every operation, the heart's action was carefully noted; and one reason for performing pneumectomy upon the left side was that the heart was directly under the operator's vision during the procedure. In only one animal of the entire series was there a spontaneous cardiac upset during operation. In this, a very old dog, a marked dilatation of both auricles and of the right ventricle was noted immediately on opening the chest. The heart's action was very slow, and it was questionable in our minds whether we ought to proceed with the experiment. Just at the completion of the pneumectomy the heart stopped beating. After direct massage of the heart the cardiac beat returned and the operation was completed. The animal recovered and was sacrificed eight months after operation. At our repeated examinations of this dog after operation, no cardiac irregularity nor dyspnea were noted. With this exception there were apparently no effects upon the heart's action from ligation of the pulmonary arteries and veins of one lung, nor from division of the main bronchus or its branches. There was no change in the cardiac movements after the lung had been removed. These statements hold true if the procedures are carried out with gentleness. It was noted in our earlier experiments that too strong traction upon the lung or bronchus, intentionally exerted, caused most commonly a slowing of the heart, followed sometimes by marked irregularity in its beat. In practically every animal in which the experiment was tried cardiac disturbances could be produced by traction upon the bronchus. The degree of inflation of the lungs also was found to have a marked effect upon the heart's action. In the dog, too little inflation most commonly caused a slowing of the heart beat, and, with the slowing of the heart there occurred very often a dilatation of the auricles. The effect upon the pulse and blood pressure of the various procedures necessary in carrying out lung excision may be seen in the accompanying tracing (Fig. 1). An examination of this tracing will show that ligation of the pulmonary arteries and veins, division of the bronchus, and removal of the entire lung, have little or no effect in dogs upon the pulse or blood pressure.

The effect of the procedure upon the respiration could not be determined during operation. So far as possible the normal respiratory rate and the normal inflation of the lung, not the object of our attack, were maintained during the experiment by the intratracheal anesthesia apparatus. At the moment the chest was completely closed by the approximation of the adjacent ribs, the remaining lung was moderately distended. The intratracheal tube was then removed and the closure of the wound completed without artificial inflation of the lung. It was commonly noted that moderate dyspnea appeared after removal of the intratracheal tube and continued for several hours. In only one animal was marked dyspnea noted. By the morning following the operation (performed in the afternoon) the dyspnea had in the majority of cases disappeared,

OPERATION  
BEGUN

CENTRAL LIGATION  
PULMONARY ARTERY  
BEGUN

Do. Tied.

PERIPHERAL  
PULMONARY

LIGATURE  
PLACED ABOUT TIED  
VEIN

MANIPULATION  
LUNG

TION  
RYISOLATION OF  
PULMONARY VEIN

Do.

*Removal of Lung*

and in the subsequent course dyspnea was never conspicuously present. The animals, kept under observation for from several months to a year, were as active as other animals, and after running about the yard showed no more dyspnea than did normal animals.

*Treatment of the Bronchial Stump.*—Although the treatment of the bronchial stump is the essential and still unsolved problem in lung excision in man, we were rather diverted from this phase of the subject and did not try a number of methods of closure which have been suggested and used by others. The procedure suggested by Henschens<sup>6</sup> of introducing a roll or plug of fascia into the lumen of the divided bronchus and closing the stump over it—quite independently thought of and successfully carried out in dogs by Dr. Halsted and later by Crowe—was not tried; nor were the various methods of fascial transplants, as suggested by Henschens and others. We did not, moreover, test the possibilities of fascial or metal bands, although a very successful result as regards occlusion and healing was obtained by the latter method. The procedures which were carried out may be grouped as follows:

1. Crushing of the isolated bronchus; closure of the divided bronchus by a single ligature of heavy (No. EE) or medium (No. C) silk, which transfixes the bronchial wall. The crushing of the bronchus with a clamp was depended upon to crush the bronchial mucous membrane. In our earlier experiments the stump after ligation and section was treated with pure carbolic acid. After cultures from the mucous membrane quite uniformly showed no organisms, this step was omitted. The bronchial stump was dropped back into the pleural cavity and purposely not covered with a fold of pleura or pericardium, in order to eliminate a covering of this sort as a factor in the healing. This method was carried out in eight animals (*L*<sup>1</sup>, *L*<sup>2</sup>, *L*<sup>3</sup>, *L*<sup>4</sup>, *L*<sup>5</sup>, *Y*<sup>1</sup>, *Y*<sup>2</sup>, *Y*<sup>12</sup>).

*Results.*—In none of the eight animals in which this simple procedure was carried out was there any leakage from the bronchial stump or pleural infection. Three of the animals are at present living and healthy about seven months after operation. Four animals died of distemper—1 one month, and 3 three weeks after operation. One animal was sacrificed eight months after operation.

*Healing of the Bronchial Stump.*—Although we intentionally did not cover the bronchial stump with a fold of pleura or pericardium, autopsy in the five animals which died or were sacrificed showed in all that the bronchial stump had retracted into the mediastinal tissues and was covered with a glistening membrane which could not be differentiated from the mediastinal pleura. The covering of the stump was often so perfect that not even a scar of any sort indicated its location, and only by traction upon the trachea could its position be determined by the dimpling of the pleura. In some of the specimens the position of the stump could be recognized by the silk ligatures which were visible through the glistening overlying membrane. In only one animal of this group was there

a scar upon the mediastinal pleura sufficiently large to show in a photograph (Fig. 2, *a*). When the bronchial stump is dissected out carefully, its end is found either smoothly rounded or more commonly bulbous, as if capped by a mass of fibrous tissue (Fig. 3, *A* and *B*). A mesial section of the bronchial stump invariably shows a solid obliteration of the end of the stump by scar tissue (Figs. 4, 5, and 6). The black silk ligatures can be seen embedded in the scar. The bronchial mucous membrane everywhere lines the lumen of the stump. Microscopic sections of the occluded ends of the stumps, shown in Figs. 4, 5 and 6—which may be taken as types—show the following:

*L*<sup>2</sup> (Mesial gross section, Fig. 4. Microphotograph, Fig. 7). The occluded end of the bronchus consists of a mass of fibrous tissue in which are scattered numerous fragments of cartilage. Here and there are blood vessels seen in cross-section, and almost in the center of the mass is a cleft (*a*) completely lined with bronchial mucosa and evidently either a prolongation of the lumen of the bronchus or an isolated space closed off from the main lumen. A fold of the bronchial wall (*b*) projects into the bronchial lumen and consists largely of masses of cartilage. The internal surface of the mass is everywhere covered with mucous membrane, excepting at one point where a ligature of black silk (*c*) is in the process of being discharged into the bronchial lumen. There is a marked reaction about the silk ligatures. They are surrounded by a zone of small round cells in which foreign-body giant cells are fairly numerous.

*L*<sup>3</sup> (Mesial gross section, Fig. 5. Microphotograph, Fig. 8). A very similar picture to *L*<sup>2</sup> above. Again, in the mass of fibrous tissue which occludes the end of the bronchus is a space (*a*) completely lined with mucous membrane and partly filled with cells with small round nuclei.

*L*<sup>6</sup> (Mesial gross section, Fig. 6. Microphotograph, Fig. 9). Again, a very similar picture to *L*<sup>2</sup> and *L*<sup>3</sup> above. There are fewer cartilage masses, and the fibrous tissue covering the stump is less cellular. There is a greater reaction about the silk ligatures. Seen in cross-section, each is surrounded by a wide zone of small round cells in which are very numerous foreign-body giant cells.

2. A modification of the above procedure. The attempt was made to secure a longer bronchial stump. After division of the pulmonary arteries and veins the lung tissue was stripped by gauze dissection, not only from the main bronchus but from the primary branches of the main bronchus. The two primary divisions of the main bronchus were individually crushed, ligated with a transfixion suture, and divided. When allowed to drop back, the long naked branching bronchial stump projected into the pleural cavity a distance of 3 or 4 cm. No attempt was made to cover it with pleura or pericardium. The reason for this procedure was twofold: (a) In man, it has been constantly stated that the bronchial stump is so short that any method of treatment aside from a simple mass ligature is not feasible. If that be the case, could not the lung be stripped from the main branches of the primary bronchus and these treated by the methods employed for the main

<sup>6</sup> Henschens: Experimente zur intrathorakalen Lungenchirurgie. Beitr. z. klin. Chir., 1914, XC, 373.

bronchus? (b) It was early noted that these two factors influenced the ease and therefore the safety of bronchial occlusion by the commonly employed methods—the size of the bronchi and the rigidity of the cartilages. In large old dogs the closure of the bronchial stump is a more difficult procedure than in small young animals. In the same animal the smaller the lumen and the less the rigidity of the bronchi, the easier is the occlusion; conditions which are more likely to obtain in the primary divisions of the main bronchus.

*Results.*—In two dogs ( $L^1$  N. S.,  $L^2$  N. S.) this method was employed. In one the usual care in the closure of the bronchi was exercised and heavy black silk (No. EE) was used for the ligatures. This animal recovered and was sacrificed eight and a half months after the operation. In the other, intentionally and perhaps foolishly, the bronchi were not crushed but were simply ligated with a transfixion ligature of fine silk (No. A). For a week after the operation this animal appeared perfectly well and then was found dead in his cage. Autopsy showed the wound perfectly healed; the pleura was everywhere smooth, glistening, and not injected; there was not a drop of fluid in the empty pleural cavity. On immersion of the bronchial stump in water, air forced into the trachea bubbled through a tiny point in the wall of the upper of the two bronchi. Dissection of the stump showed that the fine silk ligature had cut through the bronchial wall at one point. Death therefore was due to an acute pneumothorax from leakage from the bronchial stump.

*Healing of the Bronchial Stump.*—Although the bronchial stumps in these two animals were unusually long and projected a considerable distance into the pleural cavity, as in the above series, they had retracted and were covered by the mediastinal pleura. In the animal which died and was autopsied one week after operation, the covering of the bronchi was not quite complete. The lower of the two bronchi was completely covered by a smooth glistening membrane; the upper, however, was uncovered at its tip over an area 4 mm. in diameter. It was through this uncovered area that air escaped into the pleural cavity. An examination of Figs. 10, 11 and 12 will show the nature of the healing of the bronchial stump. Although we might expect that by this method the healing would be identical with that in Method 1, an examination of the only specimen that we have shows distinctly less scar tissue formation. The stumps of the two bronchi are nicely rounded (Fig. 10) and do not show the hard mass of scar tissue at the end of the stump noted in the previous series. A mesial section of the specimen (Fig. 11) shows the two primary divisions of the main bronchus separated by a ridge of tissue composed largely of cartilage. The end of each primary division is rounded, nicely healed, and without the mass of scar tissue seen in the examples described under Method 1. These rounded ends are made up of fibrous tissue, in thickness approximating the walls of the bronchi, covered without (externally) by the mediastinal pleura, within by the bronchial mucous membrane. On gross examination, no cartilage is present in this wall of scar tissue, and one has the impression that the walls of the bronchi previously apposed by the ligature have in part separated, the

intervening space being filled with scar tissue. In the primary subdivision to the left in the illustration a silk ligature lies free in the lumen. Microscopic section (Fig. 12) shows the septum (a) between the two subdivisions of the main bronchus provided with normal cartilage. The ends of the two subdivisions of the main bronchus have been occluded almost entirely by scar tissue. In the bronchus to the right in the illustration, no cartilage is demonstrable; in that to the left, one or two small fragments of cartilage may be seen. The bronchial mucous membrane lines the inner wall of fibrous tissue. In the healing of the bronchial stump in this case, therefore, the bronchial wall seems to have played but little part. One has the impression that the walls of the bronchus approximated by ligation, have separated, the defect being filled with scar tissue.

3. A modification of Method 2. The arteries and veins were ligated and divided, as in the preceding methods. The lung tissue was stripped from the two primary subdivisions of the main bronchus. The two secondary bronchi were individually crushed and ligated as in Method 2. The main bronchus and the two secondary bronchi were then crushed so as to destroy the mucous membrane, and the main bronchus inverted or folded upon itself longitudinally. This procedure brought the two secondary bronchi into apposition. The apposed walls of the main bronchus were fastened together by a series of interrupted fine silk sutures; the apposed secondary bronchi were sutured together with mattress sutures.

*Results.*—Only one animal ( $L^3$  N. S.) was treated by this method. The procedure was carried out on a large dog and was quite feasible. The animal died two and a quarter months after operation. At autopsy the wound was entirely healed and the scar quite invisible. The left pleural cavity was without a drop of fluid and the pleura showed no evidence of infection. The right lung was voluminous, crepitant, and on section showed no evidence of pneumonia. The abdominal viscera were normal. The animal showed a remarkable degree of emaciation, and the only explanation of his death was starvation.

*Healing.*—The bronchial stump had retracted and was covered by a smooth glistening membrane. Gross examination of the stump shows the end bulbous (Fig. 13) and, on palpation, hard and solid as if composed of fibrous tissue. The identity of the two subdivisions of the main bronchus, apposed and sutured together at the time of the operation, is quite lost. Mesial section through the stump shows an interesting picture (Fig. 14). The lumen of the main bronchus is filled by a mass which is composed largely of cartilage mixed with fibrous tissue and which represents the remains of the longitudinally inverted bronchial wall and the apposed secondary bronchi. Between the mass and the bronchial wall is a cleft lined on either side with normal bronchial mucous membrane. In other words, the inverted portion of the bronchial wall has not become adherent to the uninverted portion (probably due to insufficient crushing of the mucous membrane), and although it fills the lumen of the bronchus it does not obliterate it. The end of the bronchial stump is composed of a dense mass of

tissue in which cartilage and scar tissue are inextricably mixed and in which the identity of the two subdivisions of the main bronchus is completely lost. In this mass may be seen the silk sutures used in the closure. Microscopic section (Fig. 15) shows the end of the bronchus obliterated by a mass of tissue composed of fibrous tissue and cartilage fragments. The infolded portion of the bronchial walls is viable and fills the lower end of the bronchus but does not completely obliterate it. The clefts between the infolded and normal bronchial walls may be seen at *a* in the illustration. These clefts are lined with normal mucous membrane. Here and there in the section (as at *b*) the mucosa of the normal bronchial wall has fused with that of the infolded portion. Our conception of this method is that the infolded wall of the bronchus may quite satisfactorily occlude the bronchial lumen, but presumably will not completely obliterate it unless the bronchial mucous membrane is adequately crushed or removed.

4. The usual ligation and division of the pulmonary arteries and veins. The isolated main bronchus was bisected, the mucous membrane removed, and the two halves of the bronchus flattened together and held with a series of sutures around the edges, together with interrupted through and through sutures which encircled the cartilages. This method was described by Dr. Halsted<sup>\*</sup> and his success with it led us to dismiss it after one experiment.

*Results.*—The method was used in one animal (*L*<sup>4</sup>). He recovered from the operation but died three months later from distemper. Autopsy showed the external wound perfectly healed. The pleura was glistening and not injected. There was no fluid in the left pleural cavity. The stump had retracted, was covered with a glistening membrane and was quite invisible. Tested for in the usual way, there was no leakage. The right lung showed an extensive bronchopneumonia. There was a small amount of free cloudy fluid in the right pleural cavity.

*Healing.*—The retraction and covering of the stump by the mediastinal pleura had occurred as in the previously described methods. On dissection of the stump it was found capped by a mass of scar tissue (Fig. 16). A medial section of the stump (Fig. 17) shows its total occlusion by a mass of scar tissue, in the center of which may be seen the cartilages of the apposed bronchial walls. The scar tissue is therefore extra-bronchial and not intrabronchial. The silk sutures are seen in this scar tissue outside the apposed bronchial walls. Microscopic section (Fig. 18) shows the occluded end of the stump composed of fibrous tissue, in the center of which are seen in section the cartilages apposed at the time of operation. As compared with sections by Method 1, the scar tissue lies in general external to the cartilages rather than being intermixed with cartilage masses. The mucosa lines the lumen of the bronchus completely, excepting at one point where again a ligature apparently is in process of being discharged into the bronchial lumen.

\* Halsted, W. S.: Clinical and experimental contribution to the surgery of the thorax. *Trans. Am. Surg. Ass.*, 1909, XXVII, 119.

5. Isolation of the main bronchus; crushing; ligation with a transfixing ligature of medium or heavy silk. Carbolization of the stump. Inversion of the stump under a purse-string suture or several sutures. The method is that of Willy Meyer<sup>†</sup> and is identical with the common method of treating the appendix stump.

*Results.*—The bronchial stumps in nine animals were treated by this method (*L*<sup>5</sup>, *L*<sup>7</sup>, *L*<sup>9</sup>, *L*<sup>10</sup>, *L*<sup>11</sup>, *L*<sup>12</sup>, *L*<sup>13</sup>, *L*<sup>14</sup>, and *Y*<sup>14</sup>). The method was tested thoroughly on animals of various sizes because of the criticism by a number of authors that it only occasionally is feasible. In all the animals the method was perfectly feasible, although it became more difficult the larger the lumen of the bronchus and the greater the rigidity of its walls. One of the dogs is at present living and healthy, seven months after operation; two animals sent to the farm for the summer were lost, one of which was known to be living ten months after operation, the other, three months after operation. One animal died three weeks after operation. At autopsy there was no infection of the parietal wound or pleura, nor leakage from the bronchial stump. Death was due to pneumonia of the remaining lung. The remaining five animals were sacrificed at varying intervals up to one year after operation.

*Healing.*—Dissection of the bronchial stumps showed in some a bulbous end (Fig. 19), in others a tapering or rounded end (Fig. 20). Mesial sections of the bronchial stumps show in all a very satisfactory occlusion of the stump. The interesting features observed in the healing by this method may be seen in Figs. 21 to 25, showing five of the specimens. The first (Fig. 21) is a beautiful example of a perfectly inverted stump. The walls of the inverted portion of the bronchus, apposed by the ligature, have remained in contact with each other and have solidly united. The bronchial mucous membrane covers the inverted portion of the bronchus. The purse-string sutures may be seen embedded in the scar tissue which caps the bronchial stump. In the second, Fig. 22 (animal sacrificed one year after operation), the healing is similar, but with the difference that the inverted portion of the bronchial wall has become flattened down and greatly thinned as compared with that in the preceding specimen. The specimen is interpreted as a later stage of healing by this method than in the preceding specimen. An examination of the third (Fig. 23) (from an animal dying three weeks after operation from pneumonia) shows that the walls of the inverted portion of the bronchus (*a*) previously apposed by the ligature, have separated, the space between them forming a cavity (*b*), which communicates with the lumen of the trachea and which is lined with granulation tissue and partly filled with a mass of silk. A fairly broad and solid mass of scar tissue separates the cavity from the exterior, and although the healing is incomplete and imperfect, it is quite effective. In the fourth (Fig. 24) (from an animal dying two weeks after operation from distemper) similar conditions obtain; but here the cavity formed by the separation of the previously apposed inverted bronchial walls (*a*)

† Meyer, Willy: Pneumectomy with the aid of differential air pressure; an experimental study. *J. Am. M. Ass.*, 1909, LIII, 1978.

has become partially, though not completely, filled with scar tissue. In the fifth (Fig. 25) (from an animal sacrificed seven months after operation) what appears to have been a space between the separated inverted bronchial walls has become filled with a solid mass of scar tissue which quite occludes the entire short bronchial stump. A narrow cleft (*a*) lined with mucous membrane separates the inverted from the noninverted portions of the bronchial wall. In this group of cases healing took place either perfectly, as shown in the first or second specimen, or imperfectly, the succeeding stages of which are shown in the third, fourth, and fifth specimens. Microscopic sections confirm our interpretation of the gross specimens, with one exception. In the section (Fig. 26) of the specimen shown in Fig. 21, the occluded end of the stump consists of a mass of scar tissue which lies completely below the cartilages of the inverted stump. The cartilages of the bronchus can be readily followed into the inverted portion of the stump. There is no intermingling of cartilage and fibrous tissue, as seen in Method 1. The scar tissue caps the inverted portion of the stump and fills the space between the inverted walls. The mucosa completely lines the inverted stump. In the section (Fig. 27) of the specimen shown in Fig. 22, the inverted portion of the bronchial stump has become flattened down. The cartilage masses are very much less in evidence. The occluded end of the bronchus is made up largely of dense fibrous tissue. In the section (Fig. 28) of the specimen shown in Fig. 23, the walls of the inverted portion of the stump have been separated widely so that the inverted portion of the bronchial wall (as seen in section) is almost in contact with the uninverted portion on either side. There is, therefore, a wide space or cavity between the inverted walls of the bronchus which communicates with the lumen of the bronchus. This cavity is filled with a mass of silk and blood clot (*a*). Evidently the silk is about to be discharged into the bronchus. Below this cavity and separating it from the exterior is a broad firm mass of scar tissue. The cavity is lined, not with mucosa but with granulation tissue. What has apparently happened in this case is that the ligature about the inverted stump has slipped off or cut through, allowing the inverted walls of the bronchus to spring apart. The closure of the stump, however, from the standpoint of adequacy is satisfactory. In the section (Fig. 29) of the specimen shown in Fig. 24, the walls of the inverted portion of the bronchus are again seen to have sprung apart. What was evidently a space or cavity between the separated bronchial walls has become partly filled with newly formed granulation or scar tissue which is abundantly vascularized. The mucosa almost completely covers this newly formed tissue. The same process has therefore apparently occurred in this specimen as in the above, but may be interpreted as a later stage in the healing. In the section (Fig. 30) of the specimen shown in Fig. 25, we find that our interpretation of the gross specimen in this case would seem an error. The central portion of the inverted stump consists of a mass of cartilage fragments, external to which is a layer of loose fibrous tissue covered completely by mucous membrane. The ligature (*A*) lies external to the cartilages of the inverted stump and

evidently has not cut through. The walls of the inverted stump therefore have not separated and the healing is as perfect as in the first two specimens described above.

6. After crushing and ligating the bronchus, a metal band, such as has been used by Dr. Halsted in his arterial work, was placed around the bronchus and tightly rolled. In a second instance, a metal band after being rolled, was flattened with a crushing clamp, and, although the impropriety of the procedure was recognized as soon as it had been done, the band, nevertheless, was left in place.

*Results.*—The procedure was carried out in two animals (*L<sup>8</sup>* N. S. and *L<sup>10</sup>* N. S.); in one the band was tightly rolled, in the other it was flattened with a crushing clamp. The animal in whose case the band was rolled recovered and was sacrificed six months after operation. The animal in whose case the band was flattened died four days<sup>8</sup> after operation. At autopsy the pleural cavity contained a considerable amount of bloody purulent fluid. The bronchial stump showed a necrosis of its wall at the upper (proximal) edge of the band with a perforation 3 mm. in diameter.

*Healing.*—In the animal which died four days after operation the end of the stump was found uncovered by the mediastinal pleura. The metal band was partly visible but was largely covered with exudate. At the upper margin of the band there was an evident necrosis of the bronchial wall with an opening into the bronchial lumen 3 mm. in diameter (Fig. 31, *b*). On attempts to remove the metal band (Fig. 31, *a*) it was found encrusted with what appeared to be a crystalline material (specimen preserved in formalin) and had become brittle so that it broke when we tried to remove it. On removal of the metal band the tissue beneath it was of extraordinary hardness, and evidently the bronchial wall beneath the band had been converted into a solid cord. On section (Fig. 32) the tissues beneath the band (*a*) consist of a solid mass made up largely of cartilage in which the silk ligature is seen. The necrosis of the bronchial wall has occurred at the upper border of the solid cord (*b*). Microscopic section of the solid cord of tissue beneath the band (Fig. 33) shows that it is made up almost entirely of masses of cartilage, in the spaces between which is a varying amount of fibrous tissue. There is no evidence that the band has cut through the bronchial wall; and it is evident that the solid cord of tissue is the closely compressed and folded bronchial wall. The cartilage masses are clearly defined but the nuclei in the majority of the cartilage masses fail to stain. This is especially true of the marginal cartilages (those immediately under the band). In a single large centrally placed cartilage the nuclei are well stained. The impression one gathers from an examination of the specimen is that the cartilages underneath the band have died.

In the animal which was sacrificed six months after operation the stump had retracted and was covered by the glistening mediastinal pleura. On removal from the body, the stump

<sup>8</sup> Possibly the dates in our notes of this case are incorrect. It seems to us unlikely that such marked changes in the structures under the metal band could have taken place in so short a time.

was rounded and extremely hard on palpation (Fig. 34). On section (Fig. 35) the bronchus beneath the band (*a*) has been converted into a solid cord. External to the band and covering it completely is a wall of fibrous tissue 1.5 to 2 mm. in thickness; beneath it is a solid mass of tissue which completely occludes the bronchus. On gross examination of the external covering of the band no cartilage can be identified and the impression given is that the band has not cut through the bronchial wall. In the mass of tissue beneath the band cartilage cannot be positively demonstrated. Microscopic section (Fig. 36) shows the cartilage of the bronchial wall above the band turned in and approximated but not completely. The space (*aa*) is that previously occupied by the metal band. The tissue external to this band (*C*) is newly formed fibrous tissue which completely covered the band. In this layer of fibrous tissue there are no cartilage masses or other structures to indicate that the metal band has cut through the bronchial wall. Within the space (*aa*) is the solid cord of tissue (*b*) beneath the metal band. This is made up of a dense tissue with closely packed nuclei, some polymorphous, others large and granular. There are many foreign-body giant cells. Nowhere can any cartilage masses be recognized, and presumably they have undergone death and disappeared. The impression given by the examination of this section is that the metal band has not cut through the bronchial wall, that the solid cord of tissue represents the bronchial wall, but that the structures composing it have entirely disappeared and have been replaced by a conglomerate mass of fibrous tissue.

It would be of little profit to discuss at length the various methods of treating the bronchial stump used in experimental lobectomy and pneumectomy. Briefly stated, these methods may be grouped as follows:

1. A simple mass ligature in the neighborhood of the hilus (Lenhardt, Robinson, Sauerbruch); used by us in eight animals.

2. The covering of the closed bronchus with a small fragment of lung tissue (Garrè).

3. Proximal ligature of the bronchus. Incision through lung tissue near the hilus. Second ligation of bronchi presenting on the cut surface of the lung. Closure of the lung over the ligated bronchi (Tiegel).

4. A procedure similar to (3) above, but without the proximal ligature (Kawamura).

5. A transfixion ligature to close the bronchus. A second ligature (of catgut) central to this which is tied loosely (Friedrich).

6. A procedure similar to (5) above, but with a double tight ligature of silk and with covering of the stump by a fold of pericardium (Schlesinger).

7. Inversion under sutures of the ligated bronchial stump, as in the appendix operation (Willy Meyer).

8. Bisection of the bronchus. Removal of the mucous membrane. Apposition and suture of the bisected bronchial walls (Halsted).

9. Crushing of the bronchus. Closure of the bronchus with mattress sutures. Covering of the stump with a transplant of fascia lata. Covering of the stump so treated with a fold of pleura or pericardium (Giertz).

10. Division of the bronchus. Removal or not of the mucous membrane. Insertion into the lumen of a plug of fascia lata. Closure of the bronchus by ligature (Henchen, Halsted, Crowe).

The multiplicity of methods is an index first, of the inadequacy in the hands of investigators of the methods used by their predecessors; and second, of the attempt to find a method which can safely be used in man. Although no one method was given a very extensive trial, our experiments would indicate that in dogs every method indicated above—and others which we employed—are technically feasible and if carefully done even the simplest (simple transfixion ligature of the bronchus) is adequate to ensure a satisfactory closure of the bronchial stump. From a study of the gross and microscopic sections of the bronchial stumps in our series it would be difficult to state which method is followed by the most satisfactory occlusion and healing. From experimental findings alone, therefore, it is difficult to say which method may most safely be employed in man. When we review the literature of lobectomy (not resection) in man we find that a simple mass ligature has been almost universally employed, the various other methods used in experimental work being impracticable because of the shortness of the bronchial stump. That this method has been inadequate is abundantly indicated by the frequency of leakage of the bronchial stump, and by the high percentage of post-operative bronchial fistulae.

*Reaction of the Pleura Upon the Operated Side.*—A common result of experimental total pneumectomy by previous observers has been the development of a clear or slightly turbid serous or serosanguineous effusion into the pleural cavity. It has been stated to occur quite independently of infection and to be responsible for a certain mortality. A pleural effusion in the dog, if small, may readily escape detection by physical examination, but even the small effusions (less than one ounce) may be recognized by fluoroscopic examination after the lung has been removed. Owing to the lack of an X-ray apparatus in the laboratory and often the impossibility of arranging examinations at the busy X-ray department of the hospital, not every dog was followed fluoroscopically. But so far as was possible, fluoroscopic examinations were made the day following operation and on succeeding days, and we wish to thank Miss Smith and Miss Black, of the hospital X-ray department, for their assistance in this part of the work. Moreover, at the autopsies of the animals which died or were sacrificed days, weeks, or months after operation, the presence of even a drop of the fluid in the pleural cavity from which the lung had been removed was invariably carefully noted. Our observations have been quite constant. Neither in the days immediately following operation nor in the course of weeks or months after operation does, so far as we have been able to determine, any fluid, even the smallest amount, accumulate

in the pleural cavity.<sup>9</sup> When, on the other hand, infection occurs, there follows invariably a pleural effusion.<sup>10</sup> We are inclined to believe, therefore, that the pleural effusions which have occurred in the experience of others have been the result of pleural infections.

*The Fate of the Pleural Cavity on the Side of Operation and the Method of its Obliteration.*—Within two, three, or four days after operation, fluoroscopic examination shows that the heart has definitely moved over toward the empty pleural cavity. Usually within two weeks the heart is in contact with the chest wall, and by fluoroscopic examination the pleural cavity appears to be obliterated except for a cleft between the base of the heart and the apical region and a space between the apex and lower border of the heart and the costodiaphragmatic angle. In the succeeding weeks these two clefts become narrower, but, as determined by fluoroscopy, they may persist for long intervals. A recent examination of four dogs still under observation seven months after operation shows apparently these two clefts still present; in other words, that the

<sup>9</sup> We may exclude from consideration the cases quoted by other observers in which the tip of a lobe or a single lobe has been removed. In these the obliteration of a small cavity must be very prompt and the presence of fluid even a week or ten days after operation (in the absence of infection) is not to be expected, and is not noted during the days immediately following operation. After the removal of an entire lung a number of observers have commented upon the development of a pleural effusion.

Robinson and Sauerbruch (Deutsche Ztschr. f. Chir., 1909, CII, 542; Centralbl. f. Chir., 1910, XXXVII, I, 391). Of 38 total extirpations performed under positive pressure anesthesia (including those of Haecker) only four animals recovered. In 18 there occurred a marked transudation of clear or slightly turbid fluid into the pleural cavity upon the side of operation, which led in part at least to death. Since in animal experiments carried out under negative pressure this complication did not occur, the authors believed their bad results were due to positive pressure. These authors comment at length on the origin and cause of this transudate, and are convinced that it may occur in the absence of infection.

Schepelman, E. (Arch. f. klin. Chir., 1913, C, 985) states that in dogs the large cavity left after the removal of the lung at first becomes filled with a serous transudate which only later disappears with the obliteration of the cavity.

Other observers have noted the absence of a pleural effusion following total pneumectomy.

Meyer, Willy (J. Am. M. Ass., 1909, LIII, 1787). The autopsy examinations upon four animals of Meyer's series, made by F. C. Wood, showed the following: Dog 1. The left pleural cavity (from which the lung had been removed) showed a small amount of clear serum; Dogs 2, 3 and 4. No fluid in the pleural cavity. (Dogs killed, 10, 13, 18 and 30 days after operation.)

Kawamura, K. (Deutsche Ztschr. f. Chir., 1914, CXXXI, 189), states that, contrary to the experience of Robinson, Sauerbruch and Haecker, he failed to find fluid in the pleural cavity.

<sup>10</sup> Our anticipation of the development of a pleural effusion following experimental pneumectomy is the result of our experience with intrathoracic cavities in man. These have always become filled with fluid; but also have always been infected. The experience with artificial pneumothorax in the treatment of pulmonary tuberculosis shows that, in the absence of infection, large intra-pleural cavities as the result of total collapse of the lung persist for months or a year without the development of a pleural effusion.

obliteration of the pleural cavity is not yet complete (Fig. 37). We must not, however, attempt to draw too positive conclusions from fluoroscopic examinations, for the lung of the dog is so little resistant to the penetration of the X-rays that we may be mistaken in our interpretation; indeed, we think it probable that in Fig. 37, for example, the triangular space to the left of the cardiac apex is occupied by lung tissue. Examination of animals dying or sacrificed weeks or months after operation and fixed in formalin as previously described, confirms, however, in general our fluoroscopic findings. The heart first comes into contact with the chest wall, a superior and inferior space above and below the heart persists for variable time,—and may persist for months (seven or eight),—but eventually disappears (Figs. 38, a; 39, a; and 40). Obliteration of the pleural cavity from which the lung has been removed begins, then, practically immediately after removal of the lung, is largely accomplished within two or three weeks, may be complete in six to eight weeks, but may not be entirely complete for six months or more.

There are three factors which contribute toward the obliteration of the cavity: the dislocation of the heart and remaining lung toward the side operated upon, the flattening or contraction of the thoracic wall with its attendant scoliosis, and the elevation of the diaphragm. Of these the heart and lung play by far the largest rôle. In early stages of the obliteration of the cavity the heart is in contact with the chest wall and the lung has extended far beyond the midline before either of the other two factors come into play. The heart has apparently only a passive part in this process, being simply pushed over toward the affected side by the enlarging lung. While we have noticed in animals sacrificed six to eight months after operation what appears to be an enlargement of the heart, we have not sufficient evidence to say, as has been stated by one observer, that the heart undergoes hypertrophy following excision of the lung.<sup>11</sup> In the late stages of obliteration of the cavity, the superior and inferior spaces become obliterated largely by the lung. In left-sided pneumectomies, for example, the right upper lobe of the lung eventually fills the left apical region and obliterates the superior space (Fig. 39). The middle lobe often extends far to the left of the midline to fill the anterior portion of the inferior space. The larger posterior portion of this space (the space between the postero-inferior border of the heart and the costodiaphragmatic sulcus) becomes filled with the enlarged lower lobe, which curiously enough in all the animals examined herniates into the left pleural cavity through the space between the inferior vena cava in front and the vertebral column behind.

The flattening or retraction of the chest wall with its attendant scoliosis invariably appears in animals which have been kept under observation for considerable periods. It does not become evident in the dog until about a month after operation, in other words, at a time when the larger part of the cavity has become obliterated. It progressively increases, and

<sup>11</sup> Kawamura, K.: Experimentelle Studien über die Lungenextirpation. Deutsche Ztschr. f. Chir., 1914, CXXXI, 189, 222.

in animals kept under observation for seven or eight months is quite marked. It is largely confined to the upper part of the thoracic wall and rarely becomes conspicuous in the lower part of the thorax. While it causes a general diminution in the size of the thorax, it would appear to contribute chiefly toward the obliteration of the superior space (Fig. 41, A and B, and Fig. 42, A and B).

The elevation of the diaphragm has not in our experience been an important factor in the obliteration of the pleural cavity in the dog. When present, it contributes toward the obliteration of the inferior space. In the animals studied fluoroscopically the diaphragmatic movements upon the side of operation were, during the period of observation (approximately one month), synchronous with that on the opposite side, and in general of equal amplitude. Occasionally the diaphragm upon the affected side appeared relaxed and lagged behind a little in its movements. In none did the diaphragm occupy a higher position upon the side of operation than upon the contralateral side. In only two animals in the entire series has a spontaneous elevation of the diaphragm occurred following total lobe excision (Figs. 43 and 44). A high elevation of the diaphragm may be produced by division of the phrenic nerve at the time of the pneumectomy, as shown in an X-ray of a dog still living, operated upon by Dr. Holman (Fig. 45). It is interesting to note that even after division of the phrenic, neither cessation of movement nor elevation of the diaphragm occurred in this animal a month after operation. Following the removal of the lung the diaphragm eventually became immobile and occupied a high position.

*Reaction of the Remaining Lung to Lobe Excision.*—We have just noted that, following the removal of one lung, the remaining lung actually increases in size and that this increase in size contributes in large measure toward the obliteration of the opposite pleural cavity. Is this enlargement of the lung due to a simple dilatation of the alveoli analogous to emphysema or due to a hypertrophy or hyperplasia of the lung? The question is rather of academic than of practical interest. The problem presents many difficulties and will require a repetition of some of our experiments before we can hope to approach its solution. (The material gathered for

this purpose was largely lost during our period abroad). From a study of such material as we have, it would appear that in the period immediately following the excision of one lung, the alveoli of the remaining lung are dilated as compared with those of the excised lung. After a period of months, however, they appear much the same as in the control. Whether or not there is an actual increase in size of the main bronchial subdivisions, an increase in the number of the terminal bronchioles, and an actual increase in the number of alveoli per lobule (which could be interpreted as a hyperplasia); or an enlargement of the alveoli with increase in the elastic tissue and an increase in the size and number of the blood vessels (which could be interpreted as a compensatory hypertrophy), all are questions which have not yet been answered.<sup>12</sup> This part of our study may then for the present be dismissed as incomplete.

*Longevity of Animals Following Lung Excision.*—It seemed to us of interest to determine whether or not total lung excision seriously affected the future life of animals subjected to this operation. A number of the dogs were therefore kept under observation for a year. As soon as they had recovered from the operation they were turned into the yard with other dogs, and were exposed to the same vicissitudes of existence as other animals. So far as we could determine they were active, healthy, free from dyspnea, and held their own with other animals. Only one animal apparently suffered as a result of the removal of the lung. He avoided the other dogs, was not so eager as they at feeding time, and had periodic attacks of dyspnea. With this exception, we could not determine that the excision of one lung affected the activity or the probable duration of life in dogs. One of the animals became pregnant several months after operation and gave birth to a litter of seven healthy pups. This animal is still living.

<sup>12</sup> Kawamura, K. (Deutsche Ztschr. f. Chir., 1913, CXXXI, 189). This author found a dilatation of the alveoli and an increase in the elastic fibers of the remaining lung; later a hypertrophy of the alveoli and a dilatation and increase in number of the blood vessels especially the capillaries—in other words, a true compensatory hypertrophy of the lung. From the description of his technic in the preparation of his material, it would seem that errors in the interpretation of his specimens might well have occurred.

## JOHNS HOPKINS HOSPITAL BULLETIN

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXXI is in progress. The subscription price is \$3.00 per year.

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FIG. 2.—Scar (a) upon the mediastinal pleura following a total pneumectomy and indicating the location of the bronchial stump.



FIG. 3B.—A bronchial stump capped by a mass of scar tissue. Treated by Method I.



FIG. 4.—Mesial section of bronchial stump shown in Fig. 3A, to show the occlusion of the end of the bronchus.



FIG. 3A.—A nicely rounded bronchial stump treated by Method I.



FIG. 5.—Mesial section of a bronchial stump also treated by Method I. The bronchial wall has been infolded by the constricting ligature.



FIG. 6.—Mesial section of bronchial stump shown in Fig. 3B, to show occlusion.

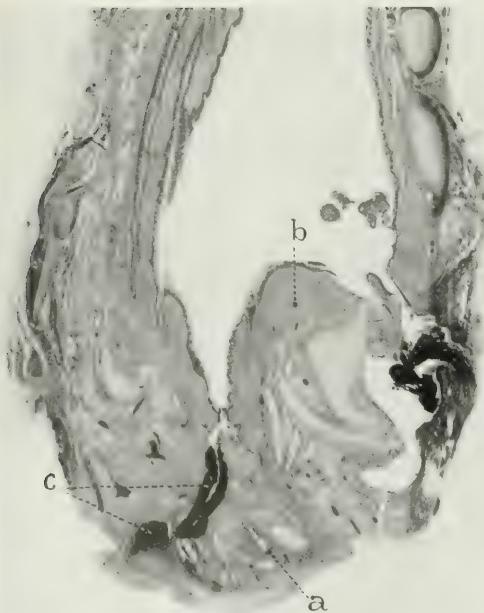


FIG. 7.—Section from specimen shown in Fig. 4. *a*, a cleft lined by mucous membrane in the occluded end of the stump. *b*, the infolded wall of the bronchus. *c*, silk ligatures.



FIG. 8.—Section from specimen shown in Fig. 5. *a*, a cleft lined with mucous membrane.



FIG. 9.—Section from specimen shown in Fig. 6. The marked reaction about silk ligatures is especially evident in this specimen.



FIG. 10.—Bronchial stump treated by Method 2. The rounded ends of the two subdivisions of the main bronchus are evident in the illustration. Animal sacrificed eight and a half months after operation.



FIG. 11.—Mesial section of specimen shown in Fig. 10.



FIG. 13.—Bronchial stump treated by Method 3.



FIG. 12.—Microscopic section of specimen shown in Figs. 10 and 11. *a*, bronchial wall at the bifurcation of the left main bronchus.



FIG. 14.—Mesial section of bronchial stump shown in Fig. 13.



FIG. 15.—Microscopic section of specimen shown in Figs. 13 and 14. *a*, cleft between the invaginated and normal bronchial wall. *b*, point of fusion of mucous membrane of invaginated and non-invaginated bronchial wall.

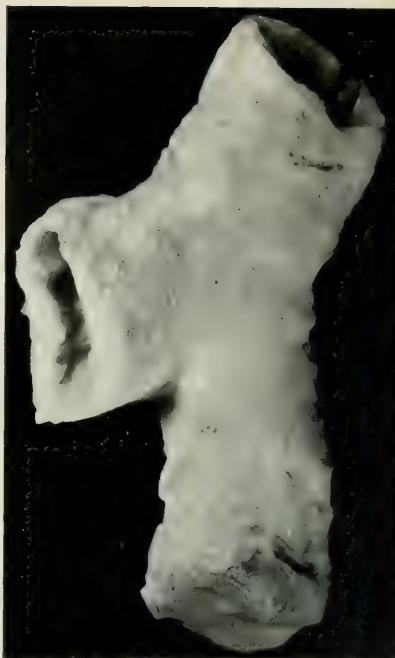


FIG. 16.—Bronchial stump treated by Method 4.



FIG. 17.—Mesial section of bronchial stump shown in Fig. 16.

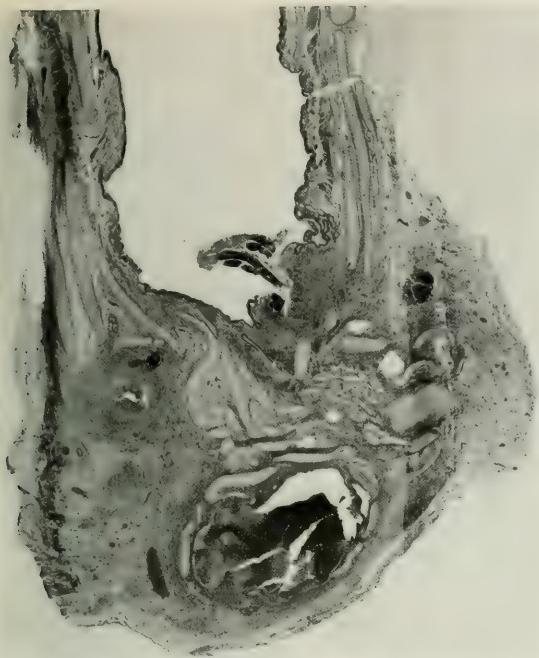


FIG. 18.—Microscopic section of specimen shown in Figs. 16 and 17.



FIG. 19.—Bronchial stump treated by Method 5 (Willy Meyer), showing bulbous end.



FIG. 20.—Bronchial stump treated by Method 5 (Willy Meyer), showing tapering end.



FIG. 21.—A perfectly healed bronchial stump treated by Method 5. Animal sacrificed three months after operation.



FIG. 22.—Mesial section of bronchial stump treated by Method 5. Animal sacrificed one year after operation.



FIG. 23.—Mesial section of bronchial stump treated by Method 5. The walls of the inverted portion of the stump (*a*) have been separated with the formation of a cleft (*b*) between them which communicates with the lumen of the bronchus.



FIG. 24.—Mesial section of bronchial stump treated by Method 5. The cleft between the separated inverted walls of the bronchus (*a*) has become partially filled with scar tissue.



FIG. 25.—Mesial section of bronchial stump treated by Method 5. The short bronchial stump is filled by a mass of tissue which completely occludes it excepting for the cleft at *a*.



FIG. 26.—Microscopic section of specimen shown in Fig. 21.



FIG. 27.—Microscopic section of specimen shown in Fig. 22.



FIG. 28.—Microscopic section of specimen shown in Fig. 23. *a*, cavity or cleft between inverted walls of bronchus.



FIG. 31.—Bronchial stump treated by Method 6. *a*, metal band. *b*, necrosis with perforation of bronchial wall.

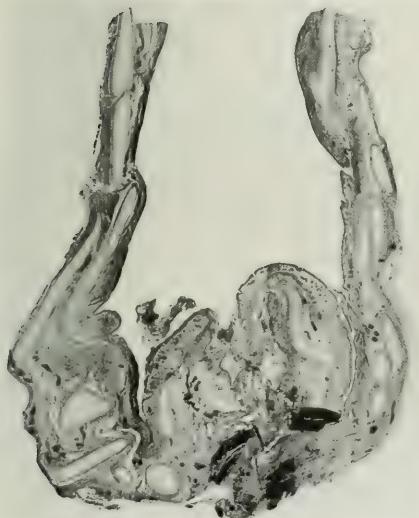


FIG. 29.—Microscopic section of specimen shown in Fig. 24.



FIG. 30.—Microscopic section of specimen shown in Fig. 25. *a*, silk ligature.



FIG. 32.—Mesial section of specimen shown in Fig. 31. The metal band has been removed. *a*, solid cord of tissue under metal band. *b*, perforation of bronchus above band.



FIG. 34.—Bronchial stump treated by Method 6.



FIG. 33.—Microscopic section of solid cord of tissue shown in Fig. 32, *a*. The mass is made up largely of cartilage, the cells of which largely fail to stain.



FIG. 35.—Mesial section of specimen shown in Fig. 34. *a*, metal band covered entirely by fibrous tissue. Beneath the band is a solid cord of tissue.



FIG. 36.—Microscopic section of specimen shown in Figs. 34 and 35. *aa*, space occupied by metal band; *b*, solid cord of tissue beneath band; *c*, fibrous tissue covering band. The metal band has not cut through the bronchial wall. Animal sacrificed six months after operation.



FIG. 37.—X-ray of animal seven months after a total left pneumectomy. The upper part of the heart is in contact with the thoracic wall. There is marked retraction of the upper thorax. The diaphragm is not elevated. The triangular space, bounded by the heart, diaphragm and thoracic wall, appears to be a true space, as seen with the fluoroscope; but is probably occupied by the lower lobe of the right lung.



FIG. 39.—Thoracic organs of an animal sacrificed five and a half months after a left total pneumectomy. The left pleural cavity is completely obliterated excepting for the cleft at *a*.



FIG. 38.—Thoracic organs (*fixed in situ*) of an animal sacrificed three months after a total left pneumectomy. The heart is in contact with the thoracic wall. The right lung has enlarged and extended toward the left. The left pleural cavity is completely obliterated excepting for the cleft at *a*.



FIG. 40.—Thoracic organs of an animal sacrificed seven and a half months after a total left pneumectomy. The left pleural cavity is completely obliterated.



FIG. 41A.—Animal five and a half months after a total left pneumectomy. The flattening of the thorax is not conspicuous.



FIG. 41B.—Same animal as in Fig. 41A. After exposure of the bony thorax the flattening of the chest upon the left side is evident.



FIG. 42A.—Animal about one year after a total left pneumectomy. The flattening of the chest is inconspicuous.



FIG. 42B.—Same animal as shown in Fig. 42A. The flattening of the chest after exposure of the bony thorax is evident.



FIG. 43.—The diaphragm seven and a half months after a total left pneumectomy. There is no elevation of the diaphragm on the pneumectomized side; the usual finding in our experience.



FIG. 45.—Elevation and immobility of the diaphragm seven months after a left total pneumectomy combined with division of the phrenic nerve.



FIG. 44. The diaphragm in an animal sacrificed five and a half months after a total left pneumectomy. The diaphragm is markedly elevated on the side of operation. It is one of only two instances in which elevation of the diaphragm was noted.

# THE EFFECT OF ARTERIOVENOUS FISTULA UPON THE HEART AND BLOOD-VESSELS

## AN EXPERIMENTAL AND CLINICAL STUDY

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Since the fall of 1914 it has been my good fortune to make with Professor William S. Halsted some experimental and clinical observations upon the blood-vessels and heart. Some of these studies<sup>1</sup> have been reported in detail, while references<sup>2</sup> to the results of observations have been made. The work was begun by studying the effect of partially occluding aluminum bands upon the larger arteries of dogs, and was stimulated by some clinical observations upon subclavian ribs, which, when they partially occluded the subclavian artery, sometimes gave rise to the formation of an aneurysm just distal to the rib. Thus begun, our work has led into various other lines. One of these was to study experimentally the effect of arteriovenous fistula on the vascular system.

Dr. Halsted was familiar with the fact that an arteriovenous fistula altered materially the size of the artery proximal and distal to the point of fistula, and had seen clinical cases in which the heart was markedly dilated and hypertrophied. With his idea in mind that the same cause might explain the two clinical observations, namely, that an artery dilates distally to a partial occlusion of its lumen, and proximally to an arteriovenous fistula, I began producing fistulae between the arteries and veins of dogs. This work has been invaluable surgical practice, and has allowed me to make some observations which I believe are sufficiently interesting to justify their record.

At first, fistulae were made between the femoral artery and vein, but these usually did not remain patent for a longer time than a few months. When the internal carotid artery and jugular vein were used there was no difficulty in getting the fistula to remain permanently patent.

The technique employed for producing the arteriovenous fistulae is described by Carrel.<sup>3</sup>

<sup>1</sup> Halsted and Reid: An experimental study of circumscribed dilatation of an artery immediately distal to a partially occluding band, and its bearing on the dilatation of the subclavian artery in certain cases of cervical rib. Partial occlusion of the aorta with the metallic band. Observations on blood pressures and changes in the arterial wall. *J. Exp. Med.*, 1916, XXIV, 271, 287.

<sup>2</sup> Halsted, W. H.: Cylindrical dilatation of the common carotid artery following partial occlusion of the innominate and ligation of the subclavian. *Surg. Gynec. and Obst.*, 1918, XXVII, 547.

Halsted, W. H.: Congenital arteriovenous and lymphatico-venous fistulae. Unique clinical and experimental observations. *Proc. Nat. Acad. Sc., Balt.*, 1919, V, 76 and *Trans. Amer. Surg. Assoc.*, 1919.

<sup>3</sup> Carrel, A.: *Johns Hopkins Hosp. Bull., Balt.*, 1907, XVIII, 18.

### EXPERIMENTS

The observations on Dog 9 are the most complete and really form the basis of the experimental study, but in order to draw attention to some points which this animal did not show, I will include short abstracts of all of the experiments.

Dog 1.—December 10, 1914. A fistula was made between the right femoral vein and artery. There was never a thrill nor a bruit present over the fistula, but an arterial pulse could be felt on both sides of it.

March 24, 1915. A second fistula was made between the right external jugular vein and the internal carotid artery. This fistula remained permanently patent and at its site there were always a distinct thrill and a loud continuous bruit.

May 17, 1915. Animal found dead. No apparent cause for death. The fistula in the neck was patent. The vein distal to the anastomosis was markedly dilated, proximally it was collapsed and very small. No change in the artery on either side of the fistula could be detected. Between the femoral vessels the fistula had closed, the lumina of the vessels remaining patent. Below the anastomosis the artery seemed slightly smaller than above it.

Dog 2.—December 21, 1914. A very small dog. A fistula was made between the right femoral vessels. At the time of the operation a distinct thrill and bruit were present. At no time following the operation was there evidence that the fistula was open. On account of distemper the animal was sacrificed on January 27, 1915. The fistula was closed and the lumen of the artery was occluded at the point of anastomosis. No thrombus on either side of the occlusion. The lumen of the vein was patent.

Dog 3.—January 4, 1915. Fistula made between the right femoral vessels. For two and one-half months the thrill and bruit persisted. Their disappearance was gradual.

May 19, 1915. Animal sacrificed. The fistula was closed by a thin membrane lined on either side by intima. At the periphery of this new membrane the continuous silk suture was visible. Both artery and vein were patent and there was no thrombosis. There was no apparent dilatation of the artery or vein on either side of the anastomosis.

Dog 4.—January 26, 1915. Large dog. Fistula made between the right femoral vessels. The leg became markedly swollen and did not return to its normal size until about two weeks after the operation. Superficial veins became prominent soon after the operation and then gradually decreased in size.

A marked thrill and bruit were present over the fistula for several months. On May 20, 1915, a small expansile swelling about half the size of a cherry was noted at the site of the fistula. Thrill and bruit were still present, but not so marked. The swelling grew larger and the signs of a fistula less pronounced, until on August 9, 1915, the swelling was the size of a cherry and had the characters of a simple aneurysm, the continuous thrill and bruit having disappeared. The aneurysm remained present but decreased somewhat in size after the fistula had closed.

June 4, 1916. Dog sacrificed. At this time, about 16 months after the fistula had been produced, the vein was found to be totally occluded by a rounded swelling which projected from the artery into the lumen of the vein. A false membrane which had closed the fistula had apparently given way to the tension of the arterial blood and thus formed the little saccular aneurysm. There was no thrombus. The artery was slightly larger on the proximal than on the distal side of the fistula. The vein, proximal and distal to the point of its occlusion by the aneurysm, was collapsed, but its lumen was not obliterated except at the site of the aneurysm.

Dog 5.—February 2, 1915. A fistula was made between the right femoral vessels. Twenty days later the dog died of pneumonia. The fistula was patent. There was no alteration in the size of the artery. The vein was dilated distal to the fistula.

Dog 6.—February 16, 1915. Fistula made between the right femoral vessels. The thrill and bruit persisted for about two months after the operation.

May 19, 1915. Dog sacrificed. The fistula was closed by a thin septum covered by intima on both sides. Both artery and vein were patent; neither was dilated.

Dog 7.—February 2, 1915. A fistula was made between the external jugular vein and the internal carotid artery of the right side of the neck. A marked thrill and loud bruit were always present.

March 5, 1915. Dog sacrificed. Fistula patent. The artery on either side of the anastomosis was not dilated. The vein distal to the anastomosis was markedly dilated, centrally the dilatation was slight.

Dog 8.—February 22, 1915.—A right carotico-jugular fistula was made. It remained open. No change in the appearance of the dog's head or eyes occurred.

June 24, 1915. Animal sacrificed. A continuous thrill and bruit were very pronounced. Distally to the fistula the vein was markedly dilated; proximally the dilatation was less. The diameter of the artery was increased on the proximal side of the fistula, while on the distal side it measured the same as before the operation.

Dog 9.—February 26, 1915. Weight 14 pounds. Fistula made between the right external jugular vein and the internal carotid artery.

For 30 months frequent observations of this dog were made. A marked thrill and a loud continuous bruit with systolic intensification were always present at the site of the fistula. Toward the end of the observations it was evident that the artery proximal to the fistula was dilated and the vein, distally, dilated up to the mandible. Facial asymmetry or change in the eyes did not occur.

The heart at first was normal; later it became enlarged and irregular in action. A cardiac murmur developed and a thrill was felt over the precordium for a few weeks before death. An electrocardiogram was made on October 13, 1916, and again on October 10, 1917 (Figs. 1 and 2).

Röntgenograms of the heart were made in the falls of 1916 and 1917 (Figs. 3, 4 and 5).

On October 29, 1917, this dog was found dead in his cage. A copy of the autopsy dictation is here given.

The dog weighs 14½ pounds. No apparent cause of death is found either externally or in any of the cavities of the body.

The fistula is patent. The right carotid artery is deflected laterally, leaving the right vagus with an enlarged accompanying vein mesially. The left carotid artery is normal, but

the left jugular vein is very large and the transverse anastomotic branch above the cricoid is huge. The artery on the proximal side of the anastomosis is much larger than on the distal side. This dilatation is apparent in the undistended artery and extends back to the aorta. When the arterial system is distended by injecting fluid into the aorta the difference is even more striking, the artery central to the anastomosis distending more than on the peripheral side. The right jugular vein is markedly dilated distal to the fistula, whereas, central to it, it is possibly smaller than normal (Fig. 6).

The heart in this case appears definitely enlarged, both *in situ* and after removal. The right ventricle is certainly thicker than normal. The valves are normal. Weight of heart, 160 gm.; tricuspid valve measures 8.75 cm.; pulmonary,

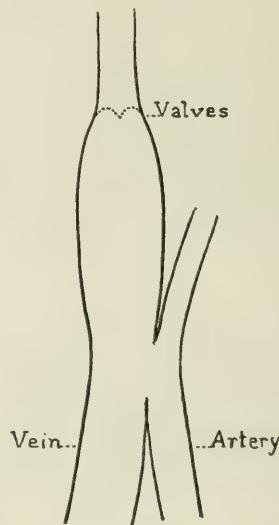


FIG. 10.—Dog. 10. External jugular vein and carotid artery, 4 months after the making of the fistula. Magnified 2 times. Note the proximal dilatation of the artery.

4.5 cm.; mitral, 7.0 cm.; aortic, 4.0 cm.; wall of left ventricle, 1.0 cm.; of right, 0.5 cm.

Dog 10.—February 5, 1915. Right carotico-jugular fistula made. Observations covered a period of four months and ten days.

June 16, 1915. Animal sacrificed under ether thus permitting observations on the vessels in life. Accurate measurements of the size of the vessels were made. The artery was dilated proximal to the fistula. Distally the vein was dilated to its first value, a distance of about 2 cm. Beyond this it was of normal size, but pulsated. Proximally, the vein was somewhat dilated to the clavicle. On opening the vessels we observed that the first valve distal to the fistula was sagged and hypertrophied but not broken. The anastomosis measured 2 mm. in diameter. No thrombosis.

Dog 11.—February 5, 1915. Fistula made in the right side of the neck. Thrill and bruit disappeared gradually in 40 days.

June 24, 1915. Dog sacrificed under ether. On both sides of the fistula the vein was collapsed. The edges of the fistula were attached to the opposite wall of the vein. There was no thrombosis in either vessel. The artery was normal.

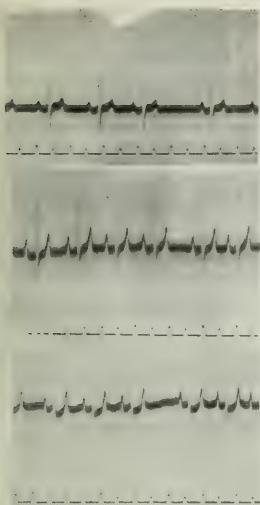


FIG. 1.—Electrocardiogram of dog 9, October 13, 1916. A fistula between the carotid artery and external jugular vein had been present for 20 months.

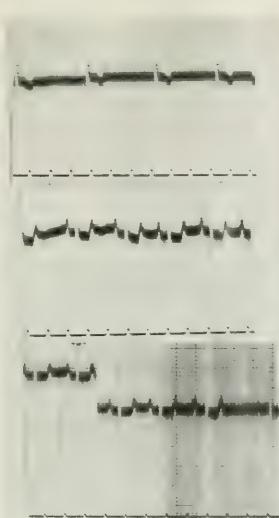


FIG. 2.—Electrocardiogram of dog 9, 12 months later.



FIG. 3.—Roentgenogram of the heart of a normal dog weighing  $17\frac{1}{2}$  pounds.



FIG. 4.—Roentgenogram of the heart of dog 9, 20 months after the fistula was produced. Weight of dog 14 pounds.



FIG. 5.—Roentgenogram of dog 9, 32 months after the fistula was produced. Note the increase in size of the heart. Weight of heart, 160 grams.



FIG. 7.—Roentgenogram of the chest of Case 1. Arteriovenous fistula between the femoral vessels had been present for many years (*vide* Fig. 8). Note the enormous size of the heart.

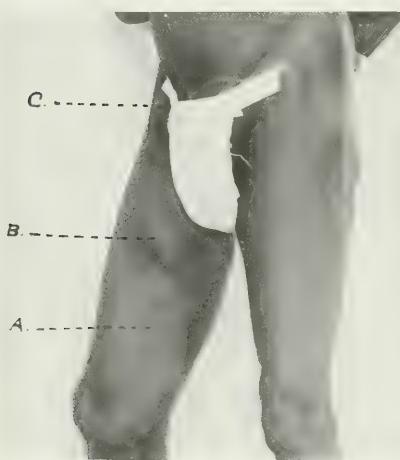


FIG. 8.—Photograph of Case 1. A, scar opposite the arteriovenous fistula. The entire artery proximal to the fistula is markedly dilated. At B and C the dilatations were so marked that they resembled saccular aneurysms. The heart of this patient was very large (*vide* Fig. 7).

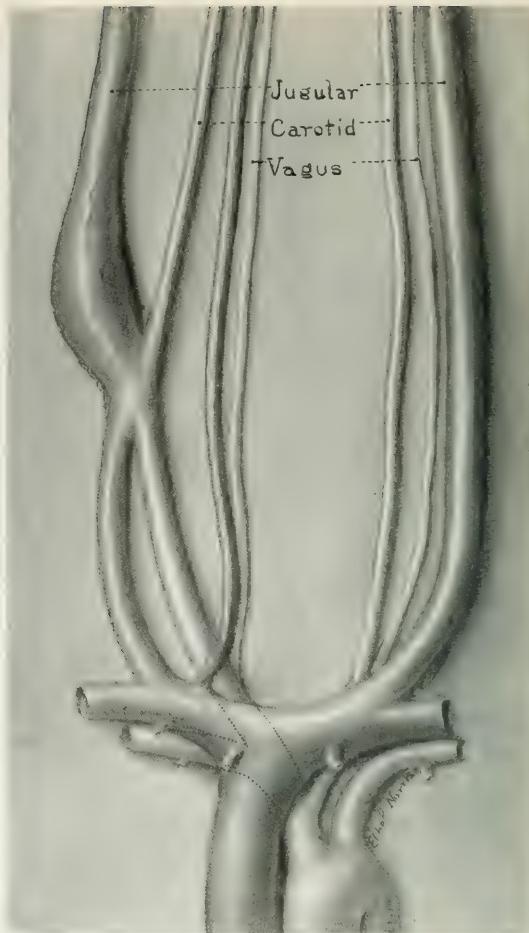


FIG. 6.—Dog 9. Actual size of the vessels distended by an equal pressure. A large accessory vein has developed by the right vagus nerve. Left jugular vein is large. Carotid artery dilated, from the arch of the aorta to the fistula. The vein proximal to the fistula was not markedly dilated, but its wall showed the most marked hypertrophy of the elastic tissue. Duration of fistula 32 months.



FIG. 9.—Actual size specimen of Case 3. An aneurysmal dilatation of the artery apposite the fistula. The artery is dilated proximally.

Dog 12.—February 5, 1915. Fistula made in the right side of the neck. The thrill and bruit remained present, but diminished markedly in intensity.

June 13, 1915. Animal sacrificed. The original fistula was closed by a thin diaphragm in the center of which was a very small opening which united the lumina of the two vessels. The artery was not dilated on either side of the fistula.

#### CLINICAL STUDY

Since the opening of The Johns Hopkins Hospital 14 cases of arteriovenous fistula have been admitted to its wards. Of these, some are so unusual and interesting that they will later be published in detail. For purposes of discussion and correlation of the clinical cases with the experimental work, short abstracts of all the cases are here given. They are studied with particular reference to the effect of the fistula upon the artery and the heart.

CASE 1.—Surgical No. 41803. A negro man of 48, was admitted October 13, 1916, with an arteriovenous fistula in Hunter's canal, on the right side. In his past life he could recall no incident that might have caused his condition. However, a very definite round scar was present in the skin just opposite the point of fistula. The patient knew that for several years, at least three, he had had a swelling in the right thigh and had observed it beating against the covers of his bed. What had brought him to the hospital was a sudden sharp pain 10 days before admission. As regards the leg, the patient said that he had paid no attention to

the swelling for he thought that everybody may have had the same thing. In his past history it was interesting to note that at the age of 25 he had had a severe hemorrhage from the urethra. The bleeding continued for eight days and following this he was in bed seven weeks. Eight years before admission a small wound on the shin of the right leg bled profusely for seven days. Five years before admission he had bled severely from a small wound of the right foot. I mention these points as evidence that the patient had probably had a fistula for years. The artery proximal to the fistula was hugely dilated and tortuous (Fig. 8). The dilatation extended above Poupart's ligament to the abdominal aorta. The heart was enlarged, extending 13 cm. to the left of the midline and 4 cm. to the right. There was a slight precordial heave and a wide area of retromanubrial dullness associated with a definite tracheal tug. There was a definite blowing systolic murmur at the apex well transmitted to the axilla. There was also a very definite forcible pulsation in the epigastric region. The Wassermann reaction was negative. *Fluoroscopic examination of the chest showed that the entire aorta was very much enlarged.*

At the operation performed October 31, 1916, by Dr. Halsted, the fistula was divided and the openings in the artery and vein were closed by lateral sutures of silk. On the proximal side of the

<sup>4</sup>Dr. Admont Clark made observations on the venous pressures of this patient both before and after operation: Before operation, right calf 19.5 cm. water; left calf 7.0 cm. water. Two months after operation, right calf 15 cm. water, left calf 15 cm. water. He regarded the pressures obtained two months after operation as normal.

TABLE 1.—A SUMMARY OF THE ANIMAL EXPERIMENTS

Dog	Position of fistula	Duration of experiment	Duration of fistula	Proximal dilatation of artery	Effect on heart	Remarks
1	Carotid artery and external jugular vein.	1 month, 23 days.	1 month, 23 days.	No.	Not noted.	
2	Femoral vessels.	1 month, 6 days.	4 (?) days.	No.	Not noted.	First observation was made a week after the operation. Fistula was then closed.
3	Femoral vessels.	4 months, 15 days.	2 months, 15 days.	No.	Not noted.	
4	Femoral vessels.	17 months, 10 days.	6 months.	Slight.	Not noted.	In this case the proximal dilatation may have decreased some in size after the fistula closed.
5	Femoral vessels.	18 days.	18 days.	No.	Not noted.	
6	Femoral vessels.	3 months.	2 months.	No.	Not noted.	
7	Carotid artery and external jugular vein.	1 month, 3 days.	1 month, 3 days.	No.	Not noted.	
8	Carotid artery and external jugular vein.	4 months.	4 months.	Moderate.	Not noted.	The dilatation was confirmed by careful measurements made at time of operation and when dog was sacrificed.
9	Carotid artery and external jugular vein.	33 months.	33 months.	Striking.	Heart markedly enlarged.	Death believed to be due to cardiac condition.
10	Carotid artery and external jugular vein.	4 months, 10 days.	4 months, 10 days.	Very definite.	Not noted.	
11	Carotid artery and external jugular vein.	4 months, 19 days.	1 month, 10 days.	No.	Not noted.	
12	Carotid artery and external jugular vein.	4 months, 13 days.	4 months, 13 days.	No.	Not noted.	In this case the fistula was almost completely closed when the dog was sacrificed.

fistula the artery was enormously dilated and showed a tendency toward sacculations, while on the distal side it was no larger than normal. There was a definite arteriosclerosis.

CASE 2.—Surgical No. 44386. A negro man of 48 years was admitted October 2, 1917. In the left thigh there was an arteriovenous fistula which had resulted from a pistol-shot wound received 12 years before admission. The typical signs developed immediately after the accident. For two years following the accident he did hard work and was not troubled except at times with a little shortness of breath and some pain in the abdomen. These symptoms were probably first noticed by the patient six months following the injury. For the next nine years the patient did light work but was bothered a great deal with increasing shortness of breath and swelling of the left leg. For the six months previous to admission his cardiac symptoms had become so marked that he had spent most of his time in bed.

The typical physical signs of an arteriovenous fistula at the apex of Scarpa's triangle were present. The artery proximal to the point of fistula was definitely dilated and could be traced with almost certainty up to the bifurcation of the aorta. The impression of this patient's condition on the medical service was chronic myocarditis, auricular fibrillation, myocardial insufficiency and marked cardiac dilatation. It was suggested that arteriosclerosis might be the cause of the heart trouble. The Wassermann reaction was negative and there was no history of syphilis; nor could there be obtained any history of rheumatism or frequent sore throats. To me it was very interesting to note that the cardiac symptoms began to develop several months after the arteriovenous fistula was produced. The cardiac condition was so bad that we did not operate on this patient.

The report of the electrocardiogram was: Auricular fibrillation.

CASE 3.—Surgical No. 6550. A laborer, 34 years old, was admitted May 21, 1897, with an arteriovenous fistula in the left popliteal space. In his past life there was a history of alcoholism and possibly a luetic infection. The Wassermann reaction was not made. The fistula had resulted from a bullet wound received eight years before admission. The signs of the fistula had developed immediately after the accident. He came to the hospital on account of swelling of his leg and localized attacks of acute pain over his heart.

The typical physical signs of an arteriovenous fistula were present. The heart was enlarged to the ninth rib on the left side. A blowing systolic murmur was present. The liver extended 2 cm. below the costal margin.

At the first operation, June 12, 1897, by Dr. W. S. Halsted, the artery proximal to the fistula was ligated. On account of gangrene due to the *B. weichii*, the leg was amputated. The specimen (Fig. 9) which had been preserved in alcohol for 20 years shows that the artery is dilated proximal to the fistula and that there is a little aneurysm of the artery just opposite to it. The sections of these vessels show an increased amount of elastic tissue in the vein, while the difference in the elastic tissue of the artery on the two sides of the fistula is not striking. The aneurysm of the artery has no elastic tissue in its wall (Plate XXV). The hypertrophy of elastic tissue in the vein seems to be more marked on the proximal than on the distal side of the fistula.

CASE 4.—Surgical No. 27731. A blacksmith, aged 55, was admitted February 9, 1911, with an arteriovenous fistula just below the right Poupart's ligament. Four months previously a piece of flying steel had produced the fistula. The heart was not enlarged and the sounds were clear.

On February 7, 1911, the vein proximal to the site of the fistula was ligated. No mention of an arterial dilatation on either side of the fistula was made. No marked changes in the physical signs of the fistula resulted from the operation.

About a month after the operation the patient had a severe attack of dizziness and vertigo, associated with nausea and vomiting. The heart then measured 12.5 cm. to the left of the midline in the fifth interspace; to the right it came to the sternal margin.

January 2, 1918. His physician writes that the patient is working at his trade. The fistula is still patent; the superficial veins in the leg are larger and a small ulcer has developed over the shin. No cardiac symptoms are mentioned.

CASE 5.—Surgical No. 32461. A negro man, 47 years old, admitted July 7, 1913, complained of numbness in the left leg and an enlarged artery.

Thirty years before admission he had been shot in the left thigh and groin with a shotgun. Following this accident the patient was perfectly well until two years before his admission when he noticed a throbbing and fluttering in his groin. A month later he noticed that his left leg tired easily and he began to walk with a definite toe drop. There was never any marked swelling of the ankle nor of the leg.

On examination the typical signs of an arteriovenous fistula were present. The heart was not enlarged.

At the operation, July 5, 1913, lateral sutures of the femoral artery and vein were made. The artery proximal to the fistula was markedly dilated while distal to it, it seemed to be contracted. The patient died from pneumonia and empyema three weeks after the operation. The operative result was excellent.

At autopsy the heart weighed 320 gm. and was normal. The artery proximal to the point of fistula measured 4 cm. in diameter and was about two times as large as the normal vessel. This dilatation did not extend to the aorta.

CASE 6.—Surgical No. 12721. A man, 19 years of age, was admitted November 26, 1901, three months after a stab wound which had resulted in an arteriovenous fistula in the left thigh. At that time his heart was normal. He was operated upon December 6, 1901. The femoral artery was ligated and the opening in the vein was sutured. At this time the vessels were noted to be small and no dilatation of the artery was present on either side of the fistula. The heart was not enlarged.

He returned January 5, 1906, five years later, complaining of weakness in the left leg. The symptoms had developed in the six weeks preceding this admission. These were extreme weakness and difficulty in walking. The aneurysm was completely healed and there was no evidence of swelling of the leg. A pulse could be felt in the left posterior tibial artery. The blood pressure in the left leg was 65 and in the right 100. The diagnosis was intermittent claudication. The heart was normal.

CASE 7.—Surgical No. 21965. A white man, 55 years of age, was admitted on February 12, 1908, for an arteriovenous fistula in the palm of the right hand. He had been struck in the palm of his hand 25 years before admission by a broken axe handle. Not until five years later did the accident bother him, but then a swelling appeared at the base of the right index and middle fingers. This swelling gradually increased in size. Pulsation had been noted for 15 years, but no pain until two weeks before coming to the hospital, when from a slight injury his hand became painful and bled.

Physical examination showed his heart to be not markedly, if at all, enlarged and the second sound was accentuated all over the heart. Marked thrill and continuous bruit were present in the swelling of the hand.

At the operation the fistula was excised. No mention is made of arterial dilatation. The patient was discharged well.

CASE 8.—Surgical No. 17168. A white man, aged 23, was admitted on December 26, 1904, for an arteriovenous fistula in the palm of the hand, particularly at the base of the middle finger. The symptoms had begun 10 years previously without any evident injury, unless they were caused by playing baseball.

The heart was not enlarged. A thrill and bruit were present in the hand. The radial artery was ligated and the vessels in the palm of the hand were partially excised. No note was made as to whether the artery was dilated. He was discharged improved.

CASE 9.—Surgical No. 13260. A carpenter, age 24, was admitted with a fractured base of the skull, on April 17, 1902. A decompression was done and a ruptured middle meningeal artery was ligated. The presence of a fistula was not suspected.

About six weeks after this operation the patient returned with a severe pain and roaring in the right side of his head. He described the noise as like that of a canary bird singing. An arteriovenous fistula was again not suspected.

May 5, 1905 (three years after the last admission), the patient returned complaining of a protrusion of the right eye and a buzzing in the head. These symptoms had gradually been getting worse since his fracture of the skull three years before. For six weeks from this admission the noise in his head, the double vision and the exophthalmos, had become so bad that he could not work. There was a remarkable pulsating exophthalmos of the right eye, a definite thrill over the entire head and a continuous murmur with systolic intensification, and a marked dilatation of the veins around the eye. The heart was normal except for a slight irregularity.

May 9, 1905. The right internal carotid artery was ligated. No note as to the size or appearance of this vessel was made. For about 15 minutes following the ligation, which was done under cocaine, the exophthalmos diminished, the arteries in the fundus became less distinct, and the thrill and noise were gone. The exophthalmos quickly returned and became even more marked than before the ligation. Other symptoms quickly returned and the patient left the hospital on May 26 unimproved.

June 17, 1907, the patient again came into the hospital with the same old symptoms, even more severe. It was noted then that the veins of the eyelid and forehead were not so large as previously. The bruit over the eye and head was less distinct. Double vision was still present. Nothing was done.

January 1, 1909, the bruit was very difficult to hear (only in front of the ear); there was very little exophthalmos; the right eye was turned by a total abducens palsy; there was no dilatation of the veins of the forehead; and the patient still heard the bruit. He was working, and in good health.

July 20, 1911, the exophthalmos was gone and the patient felt well except for headaches.

CASE 10.—Surgical No. 42514. A white man, 48 years old, was admitted April 7, 1917, with the symptoms and signs of an intracranial arteriovenous fistula. Pulsating exophthalmos was present. The symptoms had developed following a fractured skull in February, 1916. The heart was normal.

At the operation, April 18, 1917, it was noted that the internal carotid artery was unusually tortuous, but no comment was made upon the size of this vessel.

CASE 11.—Surgical No. 45360. A negro man, age 55, was admitted on March 9, 1918, for pulsating exophthalmos, due to an intracranial arteriovenous fistula. The symptoms had developed following a fracture of the base of the skull two and one-half months before admission. The case is remarkable and deserves to be made the subject of a special report. It is mentioned here to draw attention to the fact that the carotid artery at operation did not appear to be dilated. The patient's heart was not enlarged and was apparently normal.

CASE 12.—Surgical No. 18104. Male, age 31, white, was admitted August 7, 1905, for an arteriovenous fistula between the left occipital vessels. Seven years previously his head had been injured. The swelling and noise had appeared about two months after the accident. He had been operated upon four months before admission to this hospital, the occipital artery being ligated.

There was improvement, but the typical symptoms of a fistula remained. The external carotid artery was ligated August 9, 1905, and also many of the anastomotic branches leading into the varix. No mention is made of any dilatation of the carotid artery or of any abnormality of the heart.

CASE 13.—Surgical No. 28688. A white girl, at the age of 11, was admitted November 3, 1911, to this hospital for a congenital arteriovenous fistula in the right side of the neck. The heart was not enlarged. The external carotid artery proximal to the fistula was dilated. Ligation of this vessel improved but did not cure her.

At the age of 18, May 15, 1918, she returned with the fistula and symptoms about the same as at the first operation. The heart was still not enlarged. Another artery proximal to the fistula had become markedly dilated.

CASE 14.—Surgical No. 46583. A white boy, aged 18, admitted to the hospital on September 17, 1918. In the right side of his neck was an arteriovenous fistula associated with an enormous angiomatic dilatation of the veins. It had been present for five years and had developed without any apparent cause. From the character of the aneurysm and the appearance of the vessels about it, we were inclined to believe that it was a congenital arteriovenous connection. His heart was normal.

At operation a dilatation of the carotid artery was not evident; the innominate artery was not seen.

#### DISCUSSION

When the experiments were begun I was not familiar with the clinical observations in regard to the effect of an arteriovenous fistula on the artery. In fact I had thought that, as in the cases of cervical ribs, the artery might dilate distally to the fistula. A few months later it was my good fortune to help Professor Halsted to operate upon a long standing case of arteriovenous fistula (Case 1). The artery was markedly dilated for a long distance proximal to the fistula. This observation lead to a study of the literature in which were found numerous similar observations. Then we began to wonder if we might not in animals obtain experimentally results similar to those that had been observed in human beings.<sup>6</sup>

After keeping one dog for nearly three years we were pleased to find that there had been produced experimentally, for the first time, the clinical observations. In Dog 9 (Fig. 6) the artery proximal to the fistula was markedly dilated. Yet it was only toward the end of this period that it was possible to observe this by palpation. Dog 10 was kept for a period of four months and ten days, and in him a slight proximal dilatation was noted (Fig. 10). These observations agree with the clinical history of cases in human beings; namely, that it takes years for the artery to dilate proximal to an arteriovenous fistula. Distal to the point of fistula the artery gradually becomes a little smaller than normal.

I was impressed by the frequency with which experimentally produced arteriovenous fistulae close spontaneously. The fistulae between the femoral vessels invariably closed after a period of several months, while those in the neck usually remained patent indefinitely. The fistulae usually became

<sup>6</sup> A complete study by Dr. C. L. Callander of all the reported cases of arteriovenous fistula will soon appear. In this report the literature will be given fully.

TABLE II.—A SUMMARY OF THE CASES OF ARTERIOVENOUS FISTULA; ADMITTED TO THE JOHNS HOPKINS HOSPITAL

Case	Age	Position of fistula	Etiology	Symptoms	Duration of fistula	Effect on artery	Effect on heart	Remarks
Surgical No. 41803.	48	Hunter's canal.	Trauma, but history of it unobtainable.	Swelling and pain in leg.	Probably many years.	Marked proximal dilatation extending to heart.	Enlarged.	Wassermann reaction was negative. Fistula probably was present for 20 to 30 years.
Surgical No. 44386.	48	Scarpa's triangle.	Pistol shot.	Shortness of breath and swelling of leg.	12 years.	Marked proximal dilatation.	Extremely large and decompensated.	Neither in the history nor the physical findings was there anything other than the fistula to explain the cardiac condition.
Surgical No. 6560.	34	Popliteal space.	Pistol shot.	Swelling and pain in leg. Pain over heart.	8 years.	Definite proximal dilatation.	Markedly enlarged.	The leg had to be amputated on account of infection.
Surgical No. 27321.	55	Femoral region.	Piece of flying steel.	Pain in the hip and swelling of leg.	4 months.	Not noted.	Possibly slight.	A month after the operation which did not cure the patient the heart was noted to be slightly hypertrophied.
Surgical No. 32461.	47	Femoral region.	Gunshot wound.	Weakness in leg and toe-drop.	2 years and probably longer.	Marked proximal dilatation.	None.	At autopsy the heart was normal. The dilatation in the artery did not extend up to the bifurcation of the aorta.
Surgical No. 12721.	19	Femoral region.	Stab wound.	Pain and a "noise in groin."	3 months.	No dilatation.	None.	
Surgical No. 21965.	55	Hand.	Injury by handle of an axe.	Pain, swelling and noise.	20 to 25 years.	Not noted.	"Not markedly if at all enlarged."	
Surgical No. 17168.	23	Hand.	Injury by base-ball.	Swelling and pain.	10 years.	Not noted.	Not enlarged.	
Surgical No. 13260.	24	Intracranial.	Fracture base of skull.	Pain and noise in head. Protrusion of eye.	3 years.	Not noted.	Slightly irregular. Not enlarged.	It was about 6 years after the ligation of the internal carotid artery before this patient became entirely well.
Surgical No. 42514.	48	Intracranial.	Fracture base of skull.	Headache and noise in head, exophthalmos.	13 months.	"Tortuous." Dilatation not noted.	Normal.	
Surgical No. 45360.	55	Intracranial.	Fracture base of skull.	Headache and noise in head, exophthalmos.	2½ months.	Not dilated.	Normal.	
Surgical No. 18104.	31	Occipital vessels.	Injury to head.	Swelling and noise.	7 years.	Not noted.	Not noted.	
Surgical No. 28688.	18	Neck.	Congenital.	Noise in head, dizziness, swelling.	18 years.	Proximal dilatation.	Not enlarged.	
Surgical No. 46583.	18	Neck.	Congenital.	Swelling and disability.	5 years.	Undetermined.	Normal.	

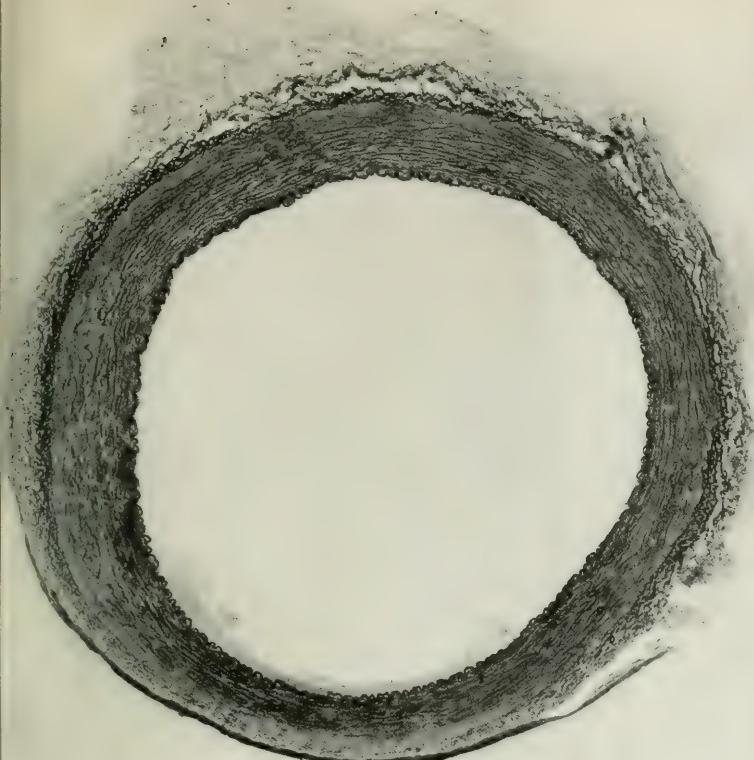


FIG. 11.—Dog 9. Photomicrograph of artery proximal to fistula. Magnified 41 times. Weigert's elastic tissue stain. Elastic tissue is not as prominent as in Fig. 12. Note the areas of apparent arring in the wall.

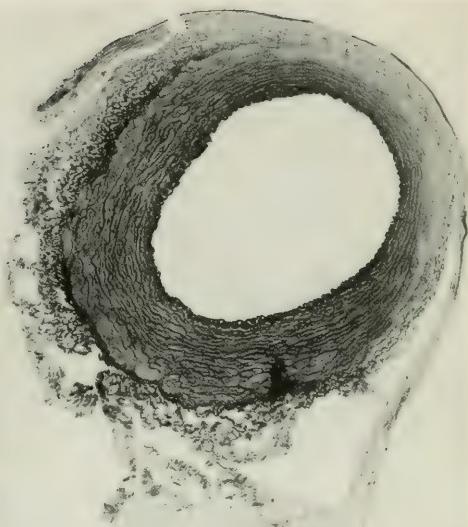


FIG. 12.—Dog 9. Photomicrograph of artery distal to fistula. Magnified 41 times. It is a little smaller than the normal artery of the left side. The elastic tissue is coarse and prominent.

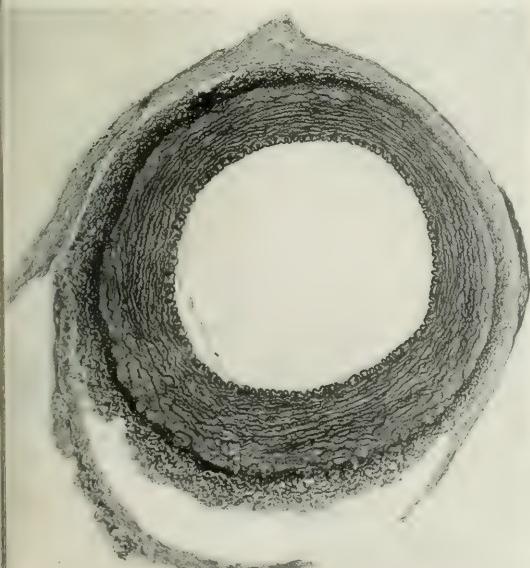


FIG. 13.—Dog 9. Photomicrograph of normal carotid artery of the left side. Magnified 41 times.

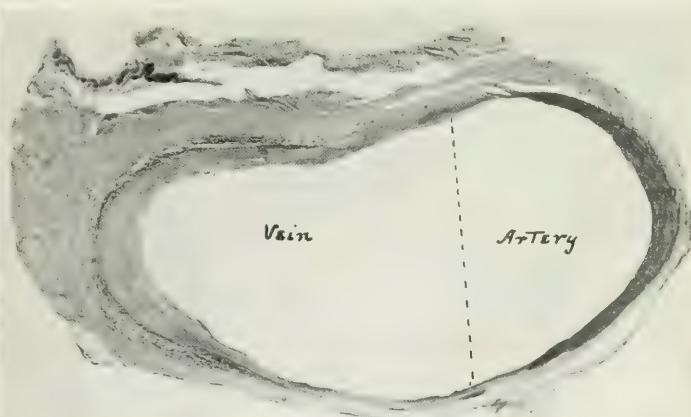


FIG. 14.—Dog. 9. Photomicrograph of section through fistula, showing vein and artery. Magnified 15 times. Duration of fistula 32 months. Note the elastic tissue of the vein.

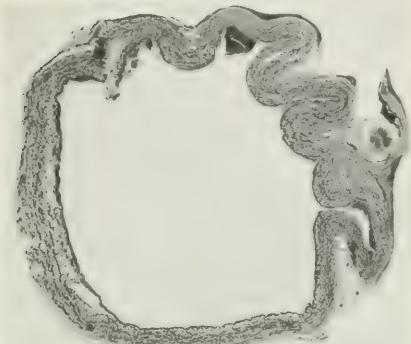


FIG. 15.—Dog 9. Photomicrograph of vein proximal to the arteriovenous fistula. Magnified 20 times. Marked increase of elastic tissue.

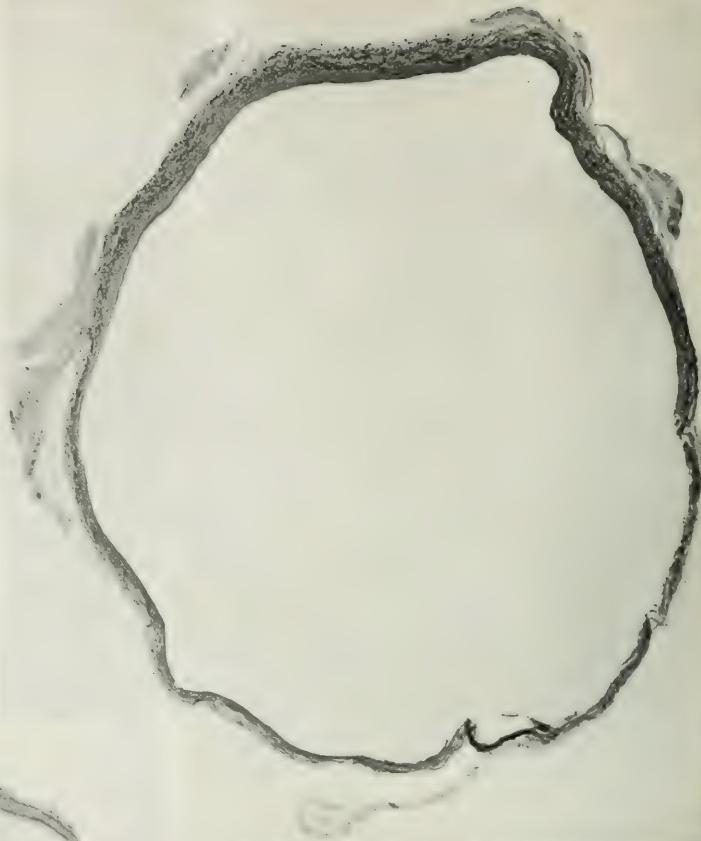


FIG. 16.—Dog 9. Photomicrograph of vein distal to the fistula. Magnified 20 times. The elastic tissue is less marked than on the proximal side of the fistula.



FIG. 17.—Dog 9. Photomicrograph of external jugular vein of left side of the neck. Magnified 20 times. The vessel is also hypertrophied due to the collateral circulation with the opposite vein.



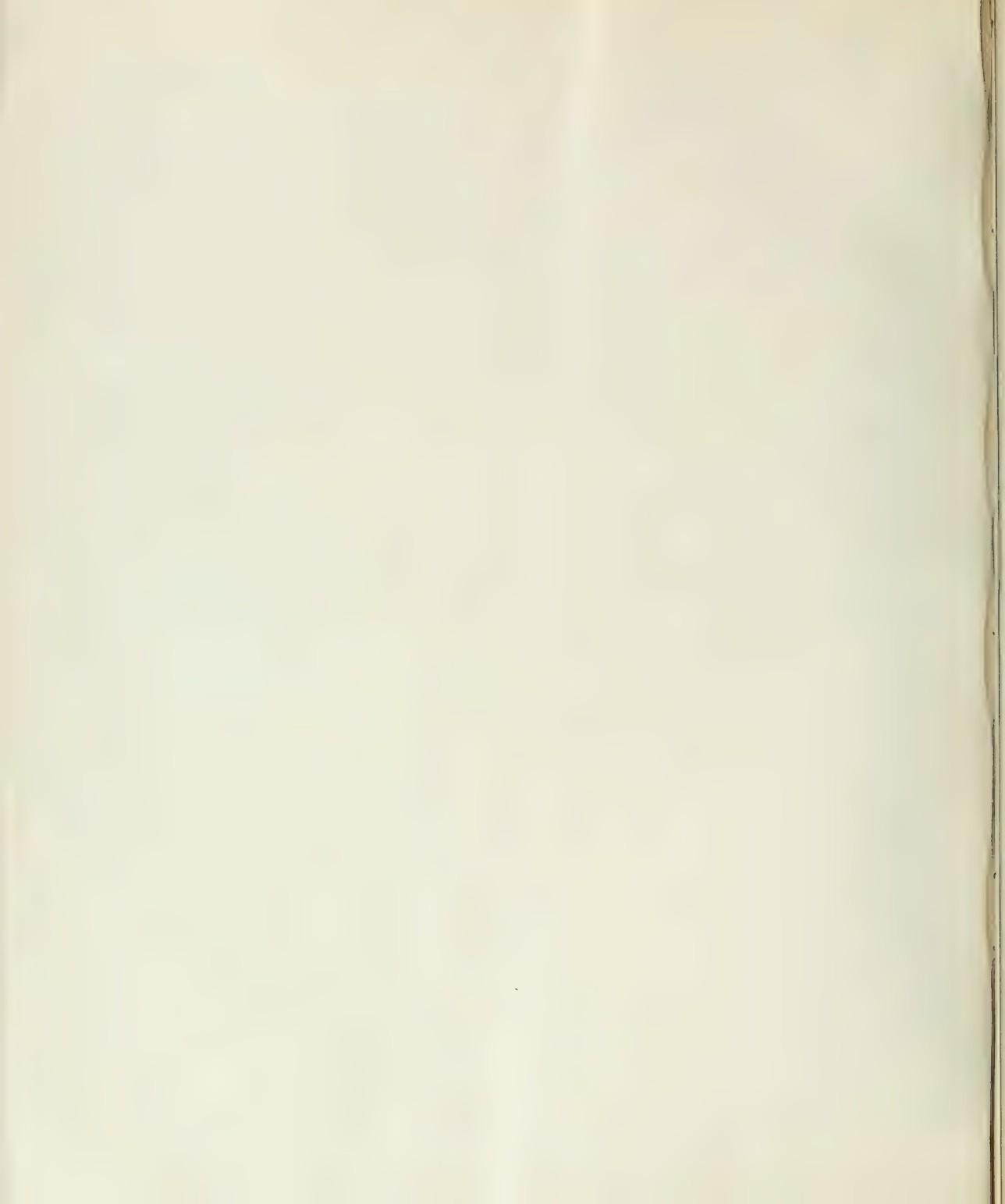
FIG. 18.—Case 3. Photomicrograph of artery and vein proximal to the fistula. Magnified 4½ times. The hypertrophied wall of the vein is evident.



FIG. 19.—Case 3. Photomicrograph through vessels at point of fistula, showing the aneurysm which developed in the artery opposite the fistula. Magnified 4½ times.



FIG. 20.—Case 3. Photomicrograph of artery and vein distal to the fistula. Magnified 4½ times. Hypertrophy of vein less marked than in Fig. 18.



closed by means of a thin septum of fibrous tissue lined on both sides by intima, while the lumina of the vessels remained undisturbed. Thrombosis, without infection, did not occur. In the femoral region the vessels lie in very close apposition, whereas in the neck the external jugular vein is widely separated from the internal carotid artery. It may be that when there is angulation at the point of fistula the blood-stream flows more directly through it, and thus tends to keep the fistula from closing. It is probable that the spontaneous closure in this series of experiments was due to the small vessels, and consequently the necessarily small fistulae, yet to me it will be very interesting to learn if many traumatic fistulae, the result of the late war, close without operative interference. The presence of the thrill and the characteristic bruit are sufficient to permit the diagnosis even when there are no other signs nor symptoms.

In a few of our cases of arteriovenous fistula (Cases 1, 2 and 3) the heart was noted to be enlarged and irregular in its action. But we could not prove that this abnormality of the heart was coincident with, or due to, the fistula. With this point in view, Dog 9 permitted some interesting observations which would indicate that an arteriovenous fistula in the neck of a dog does cause marked cardiac disturbance. Before death this dog's heart became very much enlarged, irregular in action and developed a marked systolic murmur, which was present over the entire precordium and was transmitted to the axilla and back. In the absence of any other cause for death, I am inclined to believe that this animal died of cardiac failure. An X-ray of Dog 9's heart was made 20 months after the production of the fistula, and again at the end of 32 months. In this period of a year the heart had increased markedly in size (Figs. 4 and 5). It is to be regretted that no X-rays were made before the fistula was produced. For purposes of comparison I am publishing a roentgenogram (Fig. 3) of the heart of a normal dog which weighed  $17\frac{1}{4}$  pounds, or 3 pounds more than Dog 9 weighed. If you suppose this to represent the size of the heart of Dog 9 before the fistula was produced, the marked increase in the size of its heart during the first 20 months that the fistula was present can be seen by comparing the picture with Fig. 4. Electrocardiograms of Dog 9 were made on the same days that the X-rays were taken (Figs. 1 and 2). Dr. E. B. Bridgman has very kindly commented upon these electrocardiograms for me. "Several features appear on comparison of these two tracings taken with the same standardization of current. There have been obvious changes in the pictures as shown by (1), an inversion of  $T_1$ , (2), a relative increase in the height of  $T_2$  and  $T_3$ ; (3), the appearance of  $Q_1$ , (4), the disappearance of  $S_1$  and (5), a relative change in the sequence of deviations as manifested by the  $R$  waves. There has been no prolongation of  $PR$  time, and the marked degree of sinus arrhythmia is characteristic of the normal tracings of the dog's electrocardiograms. The differences suggest myocardial changes and, perhaps, a relative hypertrophy of the right ventricle." Further convincing proof of the cardiac hypertrophy was furnished by the autopsy. The heart was markedly hypertrophied, weighing 160 gm. In a

series of normal dogs,<sup>6</sup> whose average weight was 27 pounds, the average heart weight was 145 gm. Dog 9 weighed only about half as much as was the average weight of this series, yet its heart was 15 gm. heavier. Microscopically the heart muscle showed the typical picture of cardiac hypertrophy. There was no evidence of chronic myocarditis.

Below a partially constricting aluminum band there are definite changes in the blood pressures and the structure of the vessel wall. The systolic pressure is reduced, while the diastolic pressure is increased, thus lowering markedly the pulse pressure. There is also a definite atrophy or partial disappearance of the elastic tissue in the vessel wall for a short distance below the band. These changes probably play an important part in causing the dilatation. Do the same conditions exist in the dilated artery proximal to an arteriovenous fistula? End pressures obviously cannot be taken, for in so doing the effect of the fistula on the proximal blood pressures would be eliminated. Pressures obtained through a needle introduced into the lumen of the vessel seem plausible, and experiments to determine this point are now in progress. In the dilated artery the amount of elastic tissue is less than in the artery just distal to the fistula. Owing to the dilatation, this change of elastic tissue may be more apparent than real. The histological structure of the artery distal to the fistula seems to be the same as that of the normal vessel in the opposite side of the neck. The effect of the fistula on the walls of the artery and vein is shown in the photomicrographs (Plates XXIII and XXIV).

A study of the clinical cases reveals that the artery was observed to be dilated proximal to the fistula in five instances. In seven of the cases the histories do not comment on the size of the artery. In one case in which the fistula had been present for only three months, the artery was not dilated. In Case 14 a dilatation of the innominate artery was not determined, as it was not exposed. It is interesting to note that those patients in whose history no mention is made of the size of the artery, the arteriovenous fistula was intracranial in three, in the hand in two, between the occipital vessels in one, and in the femoral region in one. In intracranial cases the surgeon has no opportunity to compare the artery proximal to the fistula with the artery distal to it, or with the normal carotid artery on the other side. This seems to me the most plausible explanation why proximal dilatation of the artery has not been noted in cases of intracranial arteriovenous fistula. Also, the duration of the fistula is usually short, as the severe symptoms drive these patients to seek aid soon after the fistula is produced. The size of the vessels involved in an arteriovenous fistula and their distance from the heart may influence the proximal arterial dilatation. In the two hand cases in which the fistula had been present for 10 and 20 years, respectively, the dilatation would probably have been noted if it had been very evident. All of the femoral arteriovenous fistulae, except the two of three and four months' duration, resulted in a proximal dilatation of the artery.

<sup>6</sup> Reid, Mont R.: "Ureterovenous anastomosis," The Johns Hopkins Hosp. Bull., Balto., 1918, XXIX, 55.

The dilatation of the artery in cases of arteriovenous fistula seems to vary directly with the duration of the fistula. The process must be very slow and gradual. Clinically it is rarely noted in the first year. Experimentally, and by means of careful measurements of the vessels, I was able to detect a proximal dilatation in two cases of four months' duration (Fig. 10).

This experimental and clinical study convinces me that grave cardiac disturbances may result from the presence of an arteriovenous fistula. Cardiac hypertrophy and dilatation due to this cause are scarcely mentioned in the medical literature. The heart of Dog 9 was markedly enlarged and death was probably due to cardiac insufficiency. In three of the clinical cases the heart was markedly enlarged, and in one case the cardiac condition was so bad that surgical treatment of the fistula was not attempted. In the absence of other causes to explain the cardiac hypertrophy in these cases is it not reasonable, in the light of the observations on Dog 9, to assume that the arteriovenous fistula may have been responsible? It may be that the proximal dilatation extends gradually all of the way to the heart. Cases 1 and 2, and Dog 9 would seem to indicate such an extensive process. In Case 5 the heart was not enlarged, and the proximal arterial dilatation did not extend to the aorta. The cardiac disturbances may not begin until the arterial change becomes extensive.

In this connection it is interesting to note that in two patients with congenital arteriovenous fistula in the neck, both aged 18 years, there was no apparent abnormality of the heart, although in one case there was a definite proximal dilatation of the artery. The adaptation of the heart to congenital vascular anomalies may be so gradual that there is no demand for an abnormal hypertrophy and dilatation. Persistent ductus arteriosus, congenital arteriovenous fistula, pulsating

naevi and patent septa of the heart may frequently be unassociated with an abnormal function or size of the heart, whereas the acquirement of these conditions after the heart has become adapted to one normal state might lead to marked, but necessary, compensatory changes. A heart that works for a congenital abnormality may not recognize it as such.

If an arteriovenous fistula will cause cardiac hypertrophy, then it seems that we may have a means of throwing some light upon the complex problem of cardiac hypertrophy. Is it due to a mechanical effect of the fistula upon the heart? May blood pressure changes be responsible for the dilatation of the heart as well as the artery? Does an increased vascular bed cause cardiac hypertrophy? Or is it nature's adaptive response to the demand of a given part for better circulation? Many other such questions could probably be studied in connection with experimental arteriovenous fistula.

#### SUMMARY

1. An arteriovenous fistula of long duration usually causes dilatation of the artery proximal to the fistula. This dilatation may extend as far as the heart.

2. Marked cardiac disturbances may result from an acquired arteriovenous fistula of long standing. They are hypertrophy and dilatation with eventual cardiac decompensation.

3. The wall of the vein involved in an arteriovenous fistula becomes hypertrophied. Although the vein on the proximal side of the fistula does not increase markedly in size, its wall shows a greater increase of elastic tissue than the wall of the vein distal to the fistula.

4. The venous blood pressure is increased in the part of the body distal to an arteriovenous fistula. When the fistula is cured the pressure returns to normal.

## THE BIOLOGICAL CLASSIFICATION OF INFLUENZA BACILLI

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Since the discovery of *B. influenzae* medical literature has become burdened with discussions about its relationship to epidemic and sporadic influenza, pneumonia, pertussis, diphtheria, measles, scarlet fever, conjunctivitis, and meningitis, whether it is really hemoglobinophilic, and whether all strains are alike morphologically, culturally and immunologically. It is very interesting reading, but, after all, the answer to many questions seems no nearer than it was almost 30 years ago. A brief review is necessary to show the exact status of *B. influenzae* and the difficulties presented in undertaking a study of this kind.

Pfeiffer<sup>1</sup> described a small Gram-negative bacillus in smears from the pharynx and the sputum of influenza patients. Later he cultivated the bacillus, finding hemoglobin essential for its growth on artificial media, and further characterized it as non-motile, aërobic, not found in the blood of influenza

patients, and not very pathogenic for animals. Afterwards he found in three cases of bronchopneumonia following diphtheria in children a bacillus in every respect the same as the one spoken of as the true influenza bacillus, with the exception that it was larger and developed many thread-like forms. This organism he called the pseudo-influenza bacillus. The differentiation was made on morphology alone. Wolff,<sup>2</sup> in 1903 stated that Pfeiffer believed all influenza bacilli were the same, and that his original idea of a pseudo-influenza bacillus was incorrect.

Cantani<sup>3</sup> thought that the pseudo-influenza bacillus and the true one were identical, and that neither of them were hemoglobinophilic, as they could be grown on media, enriched with spermicidal fluid, which did not give the spectroscopic band of hemoglobin. Ghon and Preyss<sup>4</sup> considered hemoglobin necessary even though it were present in such small quantities that

it failed to give a band with the spectroscope unless hydrazin were added. Neisser<sup>6</sup> was able to grow an influenza-like bacillus, isolated from a case of purulent conjunctivitis, on plain agar for 20 generations in symbiosis with a xerosis bacillus. Davis<sup>7</sup> thought hemoglobin, acting as a catalytic agent, was necessary for growth, and showed that a very small amount was required (1 part in 180,000 parts of medium). According to him, growth will take place in the presence of coagulated hemoglobin, but if the hemoglobin be broken up by excessive heating into hematin and globin, no growth occurs.

The difficulties which arise in the exact identification of an influenza bacillus have caused many mistakes in the past and probably will continue to cause them. Spengler,<sup>8</sup> Luzzatti<sup>9</sup> and Jochmann and Krause<sup>10</sup> have described at different times a bacillus which they considered the cause of pertussis. It is now believed they were dealing with the group of influenza bacilli and not the organism later described by Bordet and Gengou.

Gram-negative hemoglobinophilic bacilli have been recovered from different parts of the human body, also from animals, under a variety of conditions. Rosenthal<sup>11</sup> considered them ordinary members of the mouth flora without pathogenic significance. Auerbach,<sup>12</sup> Davis,<sup>13</sup> and many others have isolated them from the throats of patients with measles, pertussis, diphtheria and scarlet fever. Klineberger<sup>14</sup> described a pseudo-influenza bacillus which he isolated from pus in a gall-bladder. Cohn<sup>15</sup> recovered *B. influenzae* from a case of acute urethritis. It is generally known that these organisms may cause sinusitis, pneumonia, septicemia, endocarditis, arthritis, otitis media, and meningitis. Davis<sup>16</sup> isolated from the urine of three patients a small, Gram-negative, hemolytic, anaerobic, hemoglobinophilic bacillus. Moon<sup>17</sup> recovered a small, Gram-negative anaerobic, hemoglobinophilic bacillus from a chronic ethmoid infection. Friedberger,<sup>18</sup> working in Pfeiffer's clinic, isolated from the preputial secretions of a dog a small, Gram-negative, non-motile, hemoglobinophilic bacillus. Wolff,<sup>19</sup> working in the same clinic, isolated from the lungs of a rat a bacillus that remained exactly like *B. influenzae* for three months, after which time it acquired the property of growing on ordinary media. Pritchett and Stillman<sup>20</sup> have recovered from throat cultures a Gram-negative, non-motile, aerobic, hemolytic, hemoglobinophilic bacillus which makes milk alkaline (growth takes place when a little blood is added to the milk).

In 1905 Wollstein,<sup>21</sup> working on pertussis, isolated bacilli considered as belonging to the influenza group, but from which they could be differentiated by agglutination and absorption tests. In 1906,<sup>22</sup> not feeling so positive about this difference, she says: "The similarity of cultural characteristics of all the influenza bacilli has been emphasized by Neisser, and my experience with the agglutination reactions leads me to regard all strains as belonging to one family."

Meunier<sup>23</sup> (1897) reported 10 cases of broncho-pneumonia in young children caused by *B. influenzae*. In several instances the bacillus was recovered from the blood both before and after

death. At this time, contrary to Pfeiffer's statement, it was noted that these organisms were highly pathogenic for rabbits. Slawy<sup>24</sup> in 1899, isolated an influenza bacillus from the blood and spinal fluid of a child with meningitis. This organism was seen by Pfeiffer who agreed that it was *B. influenzae*. Cohen<sup>25</sup> (1909) recovered from the spinal fluid and blood of patients with meningitis an organism similar to the influenza bacillus, except that it caused septicemia in rabbits, and because of this difference and evidence obtained by protection experiments, he was inclined to believe that the two organisms were not the same. Thursfield,<sup>26</sup> in 1910, reported two cases of *B. influenzae* septicemia without meningitis. He agreed with Cohen and concluded by saying, "Organisms hitherto described as *B. influenzae* are not all identical, but like the coli-typhoid family, belong to a group the various members of which possess very different pathogenic powers." Wollstein,<sup>27</sup> in 1911, working with respiratory and meningeal strains, considered them identical, and varying only in virulence. Davis,<sup>28</sup> in 1911, found no difference in the virulence of respiratory and meningeal strains. Wollstein,<sup>29</sup> in 1915, still regarded all influenza bacilli as more or less identical regardless of their own origin or virulence. Davis,<sup>30</sup> in 1915, suggested dividing them into two groups, one showing the phenomenon of symbiosis, the other lacking it. Williams,<sup>31</sup> in 1919, working with a number of strains reported a few crosses by agglutination, but none by absorption tests. Huntoon and Hannum,<sup>32</sup> in 1919, say, "We have found no strains among our collection which do not show relationship either directly or indirectly through absorptions." Gay and Harris,<sup>33</sup> in 1919, found in their serological work on influenza evidence that influenza bacilli probably could be divided into groups.

In spite of the vast amount of work done, very little is known about *B. influenzae* and its biological activities. At present it is described as a small, Gram-negative, aerobic, non-motile, hemoglobinophilic bacillus. For all that is known, there may be a number of different kinds of bacilli answering that description, or there may be only one. In reality there is one true *B. influenzae* existing in name only, and that is the first one grown and described by Pfeiffer, as he did not and could not prove any of the subsequent strains to be identical with the first.

Jordan<sup>34</sup> has made the best contribution lately to our knowledge of influenza bacilli by showing that 10 of 13 strains formed indol. Owing to this discovery a study of the cultural characteristics of different strains of *B. influenzae* was undertaken. The work has not been completed, and what follows is merely a preliminary report made at this time with the hope that others will become interested and assist in the solution of the problem.

The bacilli for study were obtained from normal throats since the epidemic, 32 strains; from influenza meningitis, 5 strains (4 coming from Dr. Howland's clinic this year and 1 isolated by Dr. Wollstein in 1917); and from cases of epidemic influenza, 14 strains (supplied by Drs. Parker, Wollstein and Stillman). Two strains of *B. pertussis*, one from Dr. W. W. Ford, the other from the N. Y. Board of Health

were studied at the same time for comparison. In isolating the organisms from normal throats, all Gram-negative, aerobic, hemoglobinophilic bacilli were included in the series regardless of morphology and the kind of colony formed, since these latter vary so much under different conditions that they are unreliable criteria.

In a study of this kind it is necessary to be able to obtain at all times a vigorous growth of the organisms both on solid and in liquid media and describe their colony formation, morphology and biological activities under as favorable conditions as possible. Meat-infusion agar and broth, Ph 7.5, with from 1 to 2 per cent rabbit blood, furnish good media for growth and to which other ingredients may be added for study.

All the strains are hemoglobinophilic after at least two months of artificial cultivation, except in a few instances, in which they were grown on hemoglobin-free media in symbiosis with other bacteria for several generations. They are Gram-negative, non-motile, do not liquefy blood-gelatin, do not ferment glucose, lactose, saccharose, maltose, mannose, salicin, inulin, glycerol and xylose in one week, and, most of them, including the three hemolytic ones, have at some time shown the phenomenon of symbiosis. Three strains hemolyse rabbit blood both in liquid and in solid media.

In working with the morphology and colony formation, it is necessary to grow the various strains side by side, generation after generation, on exactly the same medium, and then it is possible to notice in a general way differences between them. Fig. 1 (magnification 8) shows colonies of four different organisms 36 hours old, grown under the conditions named above, the upper row as seen by direct light, the lower by top light. No. 1 forms indol, No. 2 forms amylase, No. 3 is hemolytic, No. 4 is *B. pertussis*. Nos. 1 and 3 are moist, become very granular and dark in the center, and when one to five days old put out daughter colonies. No. 2 is tough, holds its shape, and puts out very few daughter colonies. All pit and turn the medium a dirty brownish color. All are tan-colored after 48 hours. Older observers attributed this color to the hemoglobin in the medium, but this is unlikely as it occurs when they are grown on hemoglobin-free media in symbiosis with other bacteria. Figs. 2 and 3 (magnification 20) are copies from Pfeiffer<sup>1</sup> and Grassberger<sup>2</sup> showing the type of colonies with which they were working.

When a solid medium is inoculated with the various strains, there is seen a distinct and constant difference between the edges formed. Cultures of *B. pertussis* (Fig. 4) have elevated, smooth edges; some of the influenza bacilli (Figs. 5 and 6), elevated, lobate edges; others (Figs. 7 and 8), slightly elevated, finely irregular edges; and others which grow very delicately have no sharply defined edges. (See lower right corner of Fig. 9 which also shows two other types of cultures mentioned above, and finally *B. pertussis* in the upper right corner). Smears from cultures with the lobate edges usually show the typical small bipolar-staining bacilli called the true influenza bacillus, whereas smears from the ones with finely irregular edges and no sharply defined edges usually show

large, more easily stained bacilli, bizarre shapes, and thread-like forms. This difference is well shown by copies of Pfeiffer's<sup>1</sup> true (Fig. 10) and his pseudo-influenza (Fig. 11) bacilli.

One of the first things noticed when working with influenza bacilli was that some strains both on solid and in liquid media soon developed a perfectly characteristic fresh fecal odor. Later, when cultures of the different strains were tested for indol formation, it was found that the ones which produced this odor gave positive tests for indol when the ether extracts were layered with Ehrlich's reagent. Cultures have been distilled and ether extracts of the water-clear distillate gave the same results as were obtained before distillation. Repeated tests have been made on the various strains grown from two days to two weeks, and indol has been produced constantly by some, and not, just as constantly, by others. Thirty of the 51 strains form indol and the five meningeal ones are in the positive group. The spinal fluids of patients with influenza meningitis do not give a positive test when first drawn, but, if a tube of it be placed in an incubator for from 12 to 24 hours, a definite test is obtained. The fluid from a meningo-coccus meningitis gave a negative test when thus treated.

The ability of the various influenza bacilli to form amylase has been studied in the following manner. Defibrinated rabbit blood was added to melted meat-infusion agar which was kept at 95° C. long enough to destroy the amylase present in the blood. Then to 100 c. c. of this mixture were added from 10 to 15 c. c. of a 2 per cent sterile soluble starch solution. Plates were poured, allowed to cool and inoculated at various points with different influenza bacilli, and after from 3 to 5 days incubations were covered with a weak Lugol's solution. If the starch were not split, the medium was a dark blue up to the edge of the cultures, but if it were changed, the iodine reaction was absent around them, a colorless zone of from 4 to 8 mm. in width being left. A positive and a negative reaction are shown in Fig. 12. Nine strains produce amylase in small amounts, and none of these produce indol.

Tubes of potassium nitrate blood-broth were inoculated with influenza bacilli, incubated for 5 days, and then tested with the sulphanilic acid and naphthylamin reagent for nitrites. Thirty-three of the 51 strains have at some time given a positive reaction. Some always reduce the nitrates, others do so irregularly, while still others have never done so. This characteristic is displayed by some indol formers, by some amylase formers and by two of the three hemolytic ones. Further work may show that all can reduce nitrates under the proper conditions, making this common characteristic of the whole group, just as hemoglobin is essential for their growth.

Flasks of 100 c. c. of fat-free milk with brom-cresol purple for an indicator, and flasks of 100 c. c. meat-infusion broth with the same indicator were autoclaved separately. (If autoclaved together a precipitate forms which interferes.) After cooling, equal quantities of the milk and the broth were mixed and from 1 to 2 per cent rabbit blood was added. This is a good medium for the growth of influenza bacilli, and accurate readings can be made when an uninoculated tube is

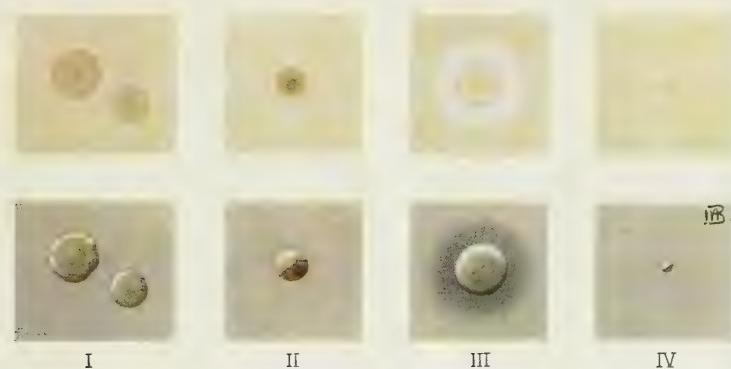


FIG. 1.

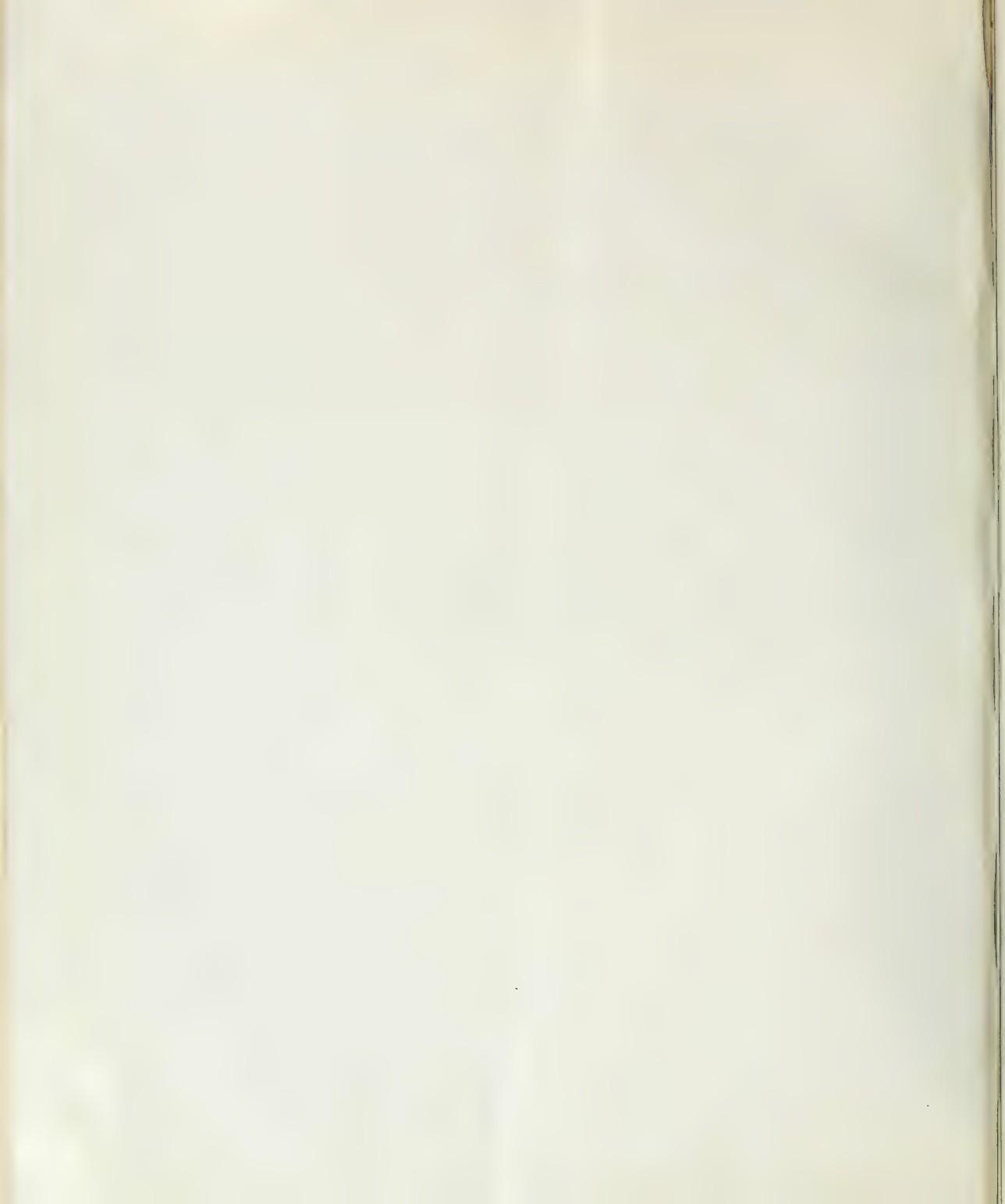




FIG. 2.

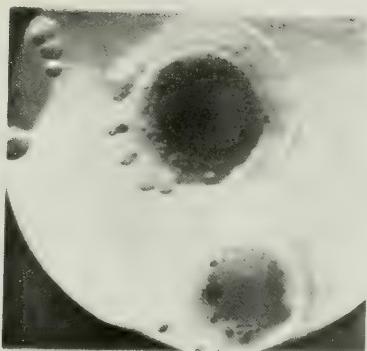


FIG. 3.



FIG. 12.



FIG. 4.



FIG. 5.



FIG. 6.



FIG. 7.



FIG. 8.



FIG. 9.

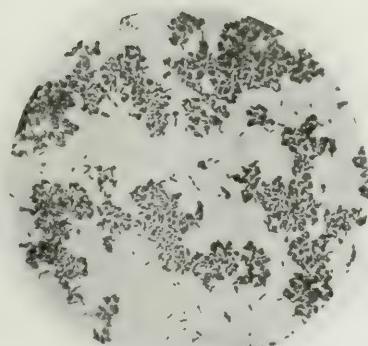
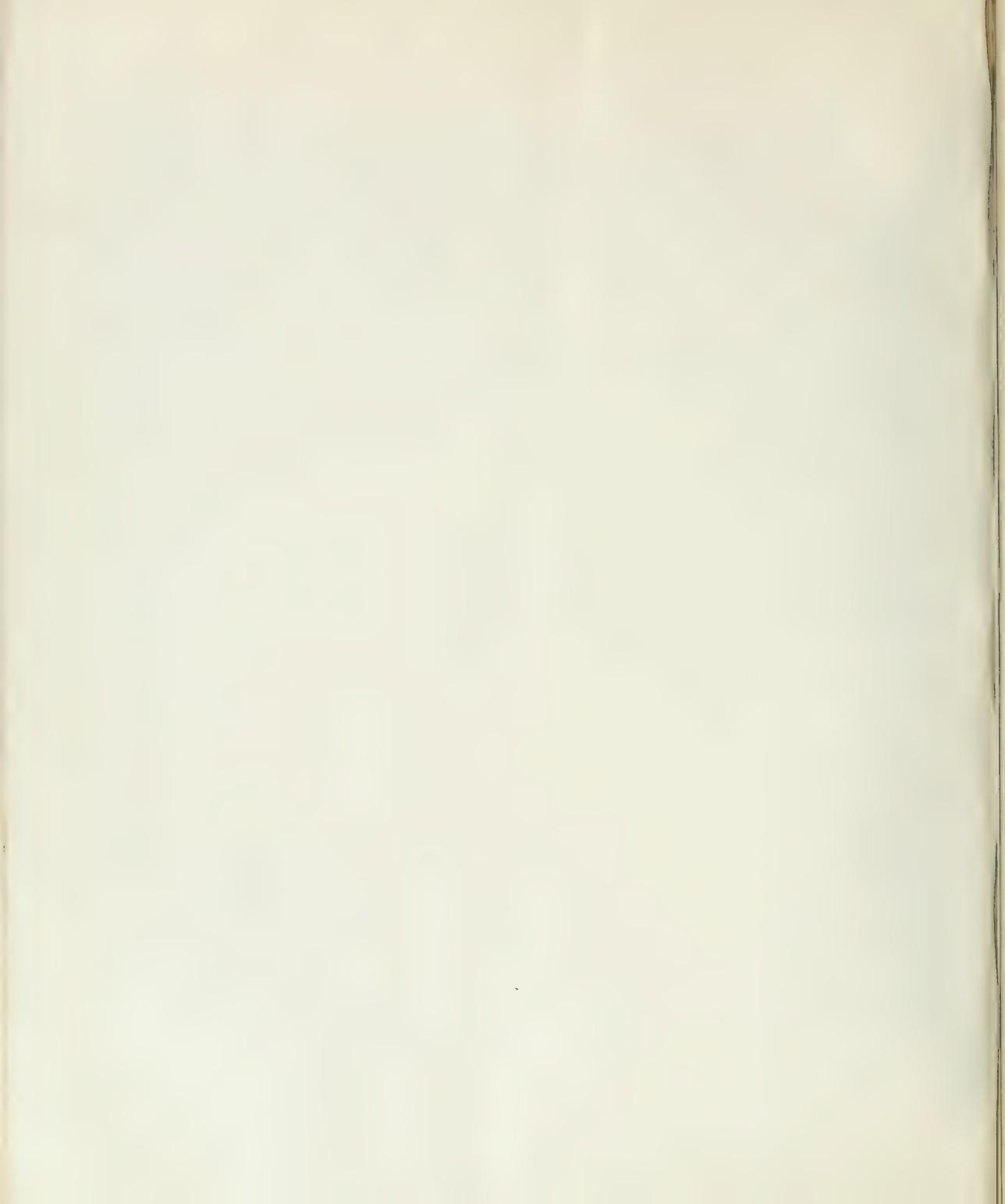


FIG. 10.



FIG. 11.



kept for a control. When these tubes of blood-broth-milk were inoculated and incubated, it was obvious very soon that all influenza bacilli are not the same culturally, as some, within 48 hours, made the milk slightly but definitely acid, others slightly but definitely alkaline, while still others gave doubtful results. This difference persisted for a week. Readings made at intervals longer than a week cannot be given at this time. The source of the acid is unknown, since lactose is not fermented.

#### DISCUSSION

Many people have never felt absolutely certain that the differences between *B. pertussis* and *B. influenzae* were sharp enough to be beyond doubt in spite of the serological proof. *B. pertussis*, after a period of artificial cultivation, can be grown on plain media, forms no indol, no nitrites and makes milk very alkaline. Some of the influenza bacilli also form no indol and no nitrites, but none of them has ever made milk nearly as alkaline as *B. pertussis*.

Time alone will tell whether these cultural characteristics will be constant. While there are differences in the biological activities of the various strains of *B. influenzae*, at the same time there are definite groups, the individual members of which are similar culturally. Only one group will be discussed at this time. It consists of 10 strains five from the spinal fluid of patients with influenza meningitis, two epidemic strains from New York, and three from normal throats. The growth and morphology of these are similar, all from indol, all reduce nitrates to nitrites, and make blood-broth-milk slightly acid within 48 hours.

Whether the strains of large bacilli that are amylase formers, or the hemolytic ones, should be included in this big influenza group is a question that will have to be decided. The nine amylase formers and the three hemolytic strains have characteristics in common with the big group, as shown by certain ones forming nitrites and by one of the hemolytic strains forming both indol and nitrites. Possibly this is a big group of organisms, like the streptococci, which have been divided into hemolytic and non-hemolytic strains, and further subdivided by cultural characteristics and serological tests. Possibly the group can be compared with the Gram-negative diplococci, Meningococcus, Parameningococci, Micrococcus catarrhalis, Micrococcus flavus, Micrococcus pharyngis siccus, Gonococcus and others.

#### CONCLUSIONS

1. The Gram-negative, non-motile, hemoglobinophilic bacilli can be classified biologically by reactions which admit of subdivisions of the group.
2. In working with a suspected *B. influenzae*, the following routine should be followed:
  - (a) Determination of hemoglobinophilic qualities.
  - (b) Colony formation.
  - (c) Hemolytic test.
  - (d) Gram stain.

- (e) Morphology.
  - (f) Motility.
  - (g) Indol formation.
  - (h) Reduction of nitrates to nitrites.
  - (i) Amylase formation.
  - (j) Reaction in blood-broth-milk.
3. *B. pertussis* can be differentiated from the group of *B. influenzae* by cultural characteristics.

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## AN UNRECOGNIZED PATHWAY FOR BACTERIAL INVASION OF THE RESPIRATORY TRACT

By M. C. WINTERNITZ, G. H. SMITH and E. S. ROBINSON

(From the Brady Laboratory of Pathology and Bacteriology, Yale University School of Medicine, New Haven, Conn.)

When a preliminary injury has destroyed the efficiency of the protective mechanism in the upper respiratory tract, it is easy to locate the portal of entry and to follow the course of microorganisms associated with pneumonia. But we know that inflammation of the lung can occur when no gross lesion of the upper respiratory tract exists. In the latter condition, how do bacteria reach the lung? This is the question we have sought to answer, and the results of our experience, briefly stated, indicate that in such cases the rich plexus of lymphatics within the submucosa of the trachea supplies the requisite pathway.

The theories concerned with pulmonary infection have been greatly influenced by the anatomical relations of the lungs and trachea. Naturally, the external communication of the lungs through the bronchi and trachea suggested that bacteria entered by this route and caused pneumonia. And it is well known that foreign material may reach the lung in this way; carbon particles, for example, are encountered within the pulmonary tissue at autopsy almost as a routine. The importance of this route is illustrated also by cases of aspiration pneumonia. On the other hand, the structure of the tracheal and bronchial lining, with its covering of ciliated, mucus-secreting epithelium, renders it difficult for foreign materials to reach the lung, and it is fair to assume that under normal conditions this protective mechanism is a competent one. Further-

more, evidence of the adequate nature of this protective mechanism is provided by the results of a large number of experiments in which both pyogenic organisms and tubercle bacilli were used. The inhalation of such organisms is without effect unless the respiratory tract has first been irritated or damaged. It is true, of course, that when the functional capacity of the mechanism is lost pneumonia follows. This has been clearly demonstrated in the study of pulmonary irritating gases.<sup>1</sup>

In reaching a conclusion concerning the pathway of infections to the lungs in various types of pneumonia, the difficulty has depended largely upon the fact that the disease could not be reproduced experimentally with a desirable degree of regularity and certainty. In many instances the conditions imposed by the experiment were so artificial that they might not be considered as factors in spontaneous infection. The intra-bronchial insufflation method is, of course, the one in mind. The lobar, lobular and interstitial types of pneumonia have all been produced by insufflation, and they have also been produced by needle puncture of the trachea through the skin of the neck.<sup>2</sup>

<sup>1</sup> Experimental Studies on the Lesions Produced by Poisonous Gases, M. C. Winternitz *et al.* Yale University Press, 1919.

<sup>2</sup> A comprehensive review of the literature, together with valuable contributions to this subject, has been presented by Wadsworth. Am. Jour. Med. Sci., 1904, CXXVII, 851.

From our studies of pulmonary irritating gases<sup>3</sup> and influenza,<sup>4</sup> it seemed logical to divide the pneumonias into two groups; namely, those secondary to damage of the protective mechanism of the upper respiratory tract, and those in which such damage was not demonstrable. Concerning the pathway of the infection in the latter type of the disease, no explanation has been suggested other than that noted above; namely, that the pathway of the microorganisms was through the lumen of the trachea and bronchi. As has been said, this seems unsatisfactory in view of the physiology of the larger air passages. The question of a primary invasion of the blood stream requires no historical discussion, since although evidence is at hand that early infection of the circulation occurs, an adequate explanation of how the organisms reach the blood stream has never been advanced.

The production of lobar pneumonia in monkeys by intratracheal inoculation by the needle puncture route has recently been reported by Blake and Cecil.<sup>5</sup> The question arises then: How can pneumonia be produced in this way, if as has been assumed, the epithelium of the upper respiratory tract is a competent protective mechanism? The one point of departure from insufflation in this experiment is the needle puncture of the wall of the trachea and subcutaneous tissues. This needle, though sterile on entry, is unquestionably infected when it is withdrawn, and consequently a possible path of infection to the lung may be found elsewhere than through the lumen of the trachea. The experiments recorded below indicate that this supposition is correct.

#### THE SUBMUCOSA OF THE TRACHEA AND BRONCHI AS A PATHWAY OF INFECTION TO THE LUNG

Rabbits were inoculated into the trachea through the skin of the neck by needle puncture. Pneumococci of established virulence were employed. Invariably the animals died of septicemia which began shortly after the inoculation and persisted until death. The period of survival after inoculation varied; in some instances it extended over six days. Infection of the needle path was found regularly, and in some animals the lesion involved not only the tracheal submucosa, but also the peritracheal and subcutaneous tissues. Whenever the subcutaneous tissue was involved, a severe cellulitis extended from the submaxillary to the thoracic region. Where the infection was less superficial, cellulitis and phlegmon were occasionally demonstrable in the deeper fascial planes of the neck. Sometimes the infection was confined chiefly to the submucous and peritracheal tissues, and in a few cases it was limited, except microscopically, to the submucosa itself. The inflammatory process in the submucosa could be traced grossly. From the point of inoculation it extended below the bifurcation of the trachea and into the larger extrapulmonary bronchi. In all

instances there was involvement of the thoracic viscera and serous surfaces. Pericarditis, pleuritis and mediastinitis were frequent, but their occurrence bore no absolute relationship to the extent of the inflammatory involvement of the lung itself. Frequently, several lobes of the lung were involved by a diffuse inflammatory process. Grossly, the lungs appeared more voluminous than normal, and despite their increased volume, contained much less air than usual. Occasionally, especially in animals which survived the inoculation for a relatively longer time (3 to 6 days), one of the lobes of the lung was found to be more voluminous than the others and definitely hepatized. As a rule, the consolidation was lobular. The microscopic examination corroborated the gross picture just described. In some of the sections the needle tract itself was included, and there minute damage to the epithelium of the trachea was demonstrable, together with the presence of a small amount of exudate at the point of entry. The remainder of the epithelium of the trachea and bronchi, except the epithelium of the bronchi involved in the pneumonic process, was intact; the delicate, ciliated margin could be readily seen. In contrast with the epithelial lining of normal appearance, the submucosa was greatly increased in depth, the blood vessels were injected everywhere, and an accumulation of polymorphonuclear leucocytes, fibrin, serum and even mononuclear cells could be traced from the upper portion of the trachea near the site of the inoculation into the submucosa of the larger bronchi near the hilum of the lung. From this point, the infection spread into the lung itself, and in several instances was clearly confined to the peribronchial and periarterial tissues, together with the alveoli of the lung in direct continuity with them. The inflammatory exudate involving the peribronchial and periarterial lymphatic trunks extended even to the pleural surface. Not infrequently a small fibrinous-purulent accumulation was evident upon the pleura and seemed attributable to an extension of the process from the larger structures.

These experiments, then, indicate that the infection of the lung was not caused by organisms introduced into the trachea, but followed the inoculation of the loose tissue of the submucosa, perhaps by way of the lymphatics, just as a *Streptococcus lymphangitis* of the finger sometimes follows needle puncture.

Other experiments were performed to control the fate of bacteria introduced by insufflation into the lumen of the trachea just below the larynx without damaging the mucosa. Intratracheal insufflation without injury to the delicate tissues of the larynx or trachea is not an easy task, at least when rabbits are the subject of experiment. This is attested by the frequent occurrence of blood on the end of the catheter when it is withdrawn and by the occasional death of the animal during the operation from a clot which occludes the trachea. For this reason, in these experiments every precaution was taken to prevent such damage. A catheter with a blunt rubber end and lateral opening was selected to protect the guiding stylet. However, even with strict precaution, the results of the experiments were far from what had been expected.

<sup>3</sup> *Vide supra.*

<sup>4</sup> The Pathology of Influenza, M. C. Winternitz, Isabel M. Wason and Frank P. McNamara. Yale University Press, 1919.

<sup>5</sup> Blake and Cecil, *cf.*: Papers read before the Soc. of Exp. Path., April 19, 1919; Nat. Acad. of Sci., November 19, 1919; Soc. Amer. Bact., December, 1919.



FIG. 1.—A retouched photograph of the trachea and bronchi of a rabbit (cleared by the Spalteholz method) to show the lymphatics injected with India ink.



FIG. 2.—Cross-section of trachea just beneath the larynx. The rabbit was killed with chloroform and the lymphatics were injected with India ink.  $\times 10$ .



FIG. 4.—Longitudinal section through the trachea, showing the extension of the India ink in the lymphatics of the submucosa.  $\times 55$ .

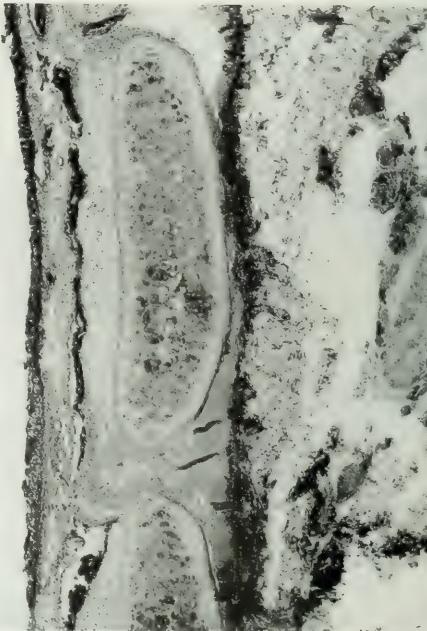


FIG. 5.—Cross-section of the trachea of a rabbit with India ink injection of the lymphatics of the submucosa. This section, taken below the bifurcation, shows injection of both bronchi.  $\times 55$ .





FIG. 6.—Section through the lung of a rabbit which had received an injection of India ink into the lymphatics of the tracheal submucosa just below the larynx. Masses of India ink are seen in the peribronchial and peritracheal tissues.  $\times 55.$



FIG. 8.—Longitudinal section of trachea showing the inflammatory reaction in the submucosa. The injection of pneumococci was given by needle puncture through an area anterior to that illustrated.  $\times 64.$

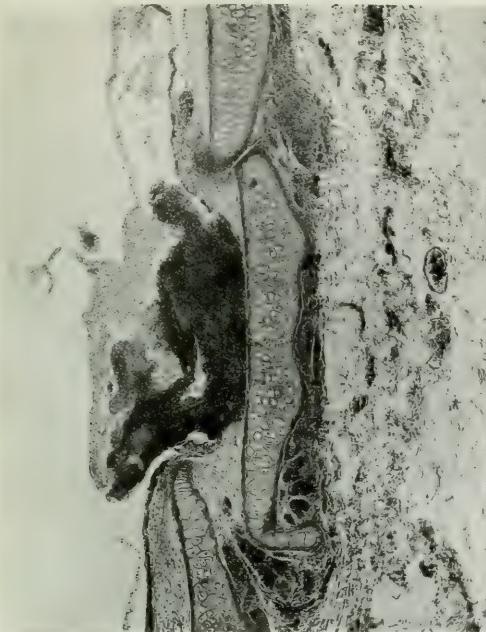


FIG. 7.—Section through the wall of the trachea of a rabbit which had received insufflation with virulent pneumococci. A plug of fibrin has formed at the point of injury.  $\times 64.$



FIG. 11.—Gram stain of the trachea of a rabbit 4 days after the intratracheal inoculation by needle puncture. The lymphatics of the submucosa are distended by masses of pneumococci. Occasional organisms are found outside of the lymphatics in the submucosa. None are to be found in the mucosa or the lumen of the trachea.  $\times 375.$

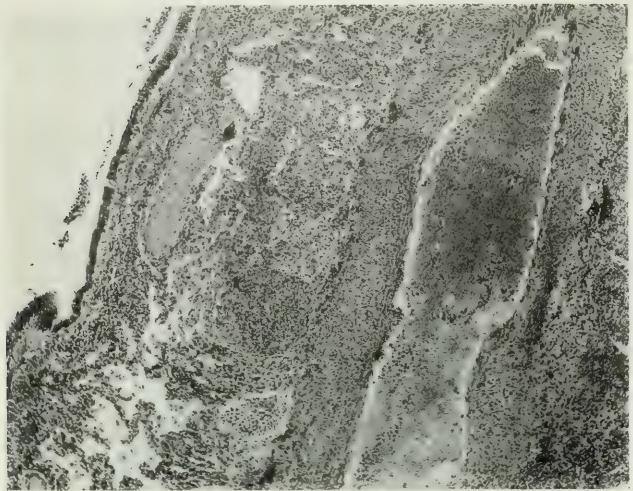


FIG. 9.—Higher magnification of the wall of the trachea. The elated margin is intact. The inflammatory reaction is confined to the submucosa. The point of injection was above this area, near the larynx.  $\times 375.$

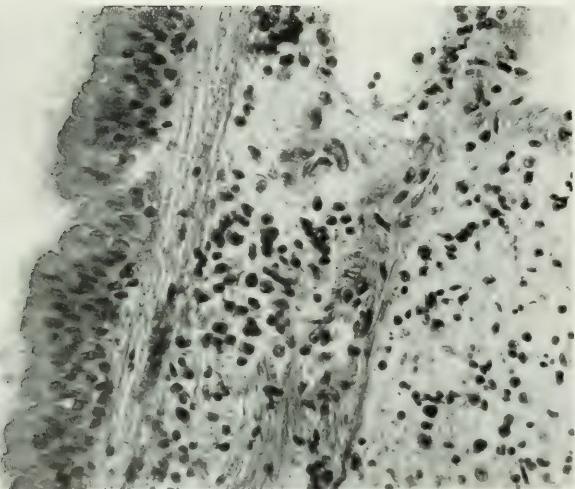


FIG. 10.—Inflammatory reaction in the lung following the inoculation of the trachea by needle puncture just below the larynx.  $\times 70.$



FIG. 12.—Higher magnification of a lymphatic shown in Fig. 11 to demonstrate the microorganisms.



FIG. 13.—High magnification of a section of the lung. The pneumococci have passed down from the point of inoculation via the lymphatic system.

In these animals the clinical course was not unlike that in animals inoculated by needle puncture. The gross anatomical findings also were identical. Mediastinitis, pleuritis and pericarditis all occurred, and while lobar pneumonia was not encountered, extensive lobular consolidation developed in many of the animals. The single point of difference between the animals inoculated by the catheter and those injected by the needle method was the absence in the former group of extratracheal inflammatory involvement in the cervical region. In no instance was there subcutaneous, intramuscular or peri-tracheal inflammation, but in all of the animals a minute lesion of the tracheal epithelium, usually just below the larynx, was seen grossly. It appeared as a small, grey, slightly opaque, friable nodule. The remainder of the epithelial covering of the trachea and larger bronchi was pale grey, translucent and occasionally slightly injected. Exudate in the lumen and marked injection of the lining membrane were found in the smaller bronchi only. Sections of the trachea through and below the point of injury, as well as those of the larger bronchi, all showed the same gross injection and thickening of the submucosal coat. Histologically, the inflammatory process in the trachea was confined to the submucosa; otherwise here, in the bronchi and in the lung, it was identical with that described above.

Occasionally, injection and even slight cellular infiltration was found in other coats of the trachea, but this was very inconspicuous. Only at one point was the lining of the trachea abnormal, and this point was the area of damage already mentioned. A few cells of the mucosa were here replaced by a plug of fibrin in which cells of the polymorphonuclear series were embedded.

This method failed to fulfil our purpose. We hoped that infection would not occur if the organisms were placed in the lumen of the trachea, but this, as we found, could be expected only if the operation caused no injury to the mucosa. Since in all of the experiments damage was done, the point of injury from the catheter served as a portal of entry for the infecting microorganisms. In fact, this series corroborated the previous one, inasmuch as the infection spread from the portal of entry through the submucosa to the thoracic viscera and involved the mediastinum, pericardium, pleura and lungs. Septicemia developed in these animals, but the point of entry of the organisms into the blood stream was not determined.

The primary object of this experiment was to demonstrate that bacteria introduced into the lumen of the normal trachea do not reach the lung. It seemed possible even that they would be mechanically carried to the oral orifice, or perhaps destroyed by the tracheal secretion, just as organisms are destroyed by the secretions of the mouth.\* Although the experiments were inconclusive in this respect, we found that whenever animals were killed or died within 48 to 60 hours after inoculation, whether inoculated by needle or by insufflation, the lumen of the trachea was sterile. The wall of the trachea, however, contained bacteria.

\* Bloomfield: The Fate of Bacteria Introduced in the Upper Air Passages. Bull. Johns Hopkins Hospital, 1919, XXX, 317.

#### THE LYMPHATICS OF THE SUBMUCOSA OF THE TRACHEA AND BRONCHI

The histological picture in the submucosa of the trachea and bronchi and in the periafteriolar and peribronchiolar alveoli of the lung suggested very strongly that the lymphatics of the submucosa of the trachea provided the pathway for the infection. However, in what way the infection spread from the submucosa of the trachea and bronchi to the pulmonary parenchyma was not clear.

It is well known that the submucosee of the trachea and bronchi contain lymphatics, though little attention has been given to these structures as compared with that given the lymphatics of the lung. The latter have been thoroughly studied, and a brief review of our knowledge of them has recently been published by Miller,<sup>7</sup> one of the chief contributors to this field. Miller divides the lymphatics of the lung into two groups: the pleural lymphatics which drain directly to the hilum of the lung, and the deep lymphatics of the lung which also drain to the hilum and communicate with the lymphatics of the pleura by short branches whose valves point towards the pleura. The pleural lymphatics contain many valves. The deep lymphatics of the lung contain few valves, all of which are near and point towards the hilum. The lymphatics of the submucosa of the cartilage-bearing bronchi may be divided into two groups: Those beneath the mucosa and those in the peribronchial tissue. These two groups communicate by short branches in the intercartilaginous spaces. In the bronchi which have no cartilage, there is only one small group of lymphatics, while the alveolar walls have none. The lymphatics of the bronchi communicate extensively with the periafteriolar system, and a large trunk is located between bronchus and artery.

The injection of the lymphatics of the submucosa we found to be simple. A needle inserted beneath the mucosa almost invariably enters a large lymphatic, and with very gentle pressure a huge plexus is demonstrable, extending up and down from the point of injection. Above, it reaches the submucosa of the vocal cords and epiglottis. Below, it is very abundant as far as the bifurcation of the trachea and extends below the bifurcation of the trachea into the larger bronchi and even into the smaller, intrapulmonary, cartilage-bearing bronchi. The injection mass diminishes markedly at the bifurcation of the trachea and at each subsequent bifurcation of a bronchus, but if the injection is commenced at the bifurcation of the trachea or even lower down, a plexus as abundant as that in the submucosa of the trachea is demonstrable. The details of the extension of the lymphatics from the submucosa of the trachea and bronchi we have not yet completely determined; the subject is now under investigation. It may be said, however, that the plexus in the submucosa of the trachea anastomoses with another plexus in the peritracheal tissue, and that large lymphatic trunks are demonstrable in this vicinity. It is also clear that relatively large branches leave

<sup>7</sup> W. S. Miller. Studies on Tuberculous Infection, III. The Lymphatics and Lymph Flow in the Human Lung. Am. Rev. of Tuberculosis, 1919, III, 193.

the trachea and bronchi at the points of bifurcation, and there is some evidence that these anastomose with the periarteriolar lymphatics. Other smaller trunks pass directly to the mediastinum, and, of course, to the glands in this vicinity.

It is necessary to assume that a short circuit occurs around the lymph glands at the hilum of the lung if the infection is carried to the lung by the lymphatics. It is known that there are few valves in the deep lymphatics of the lung and that these point toward the hilum. It is known also that the lymphatics of the submucosa of the bronchi anastomose with the peri-bronchial and periarteriolar lymphatics. A short circuit of the lymph glands at the hilum is actually provided by anastomosis of the lymphatics of the tracheal and bronchial submucosa with those of the periarteriolar and peribronchial regions. Unquestionably, other by-paths exist, but as yet these are not sufficiently defined for accurate description. However, it is pertinent that they provide paths by which infection may travel from the submucosa of the larger air passages to the lung.

The lymphatics of the submucosa of the trachea and bronchi, as we have now determined, are readily demonstrated when the tissues are stained by the Gram method after inoculation with pneumococci either by needle puncture or insufflation. The bacteria stand out prominently in the distended lymphatics of the submucosa, and although occasional organisms are seen outside of these structures, they are relatively incon-

spicuous. Furthermore, they never appear in the epithelial lining of the trachea or larger bronchi.

#### CONCLUSION

The submucosa of the trachea contains a rich plexus of lymphatics, prominent everywhere and devoid of valves. At the bifurcation of the trachea anastomosis occurs with similar plexuses in the bronchi, and this phenomenon is repeated throughout the region of the cartilage-bearing bronchi. At the bifurcation of the trachea, as well as of the bronchi, there is drainage to the lymph glands and anastomosis with periarterial and peribronchial lymphatics. When the lymphatics are injected, the largest portion of the material is diverted at these bifurcations, but continuity of the lymphatic system in the tracheal and bronchial submucosa is demonstrable.

Pneumococci introduced by needle puncture through the skin into the lumen of the trachea or by insufflation, provided the insufflating catheter damages the epithelium of the trachea, spread by way of the lymphatics to the lung. The lymphatics of the submucosa of the trachea, then, afford a direct pathway of infection to the lung. Although this lymphatic system provides a pathway for infection, it may also serve as a protective mechanism against pulmonary infection, for the drainage of the submucosa of the trachea and bronchi is largely diverted as the lung is approached to the protecting regional lymph glands.

## GERMAN NUTRITION, 1914-1919

By CLEON C. MASON,

*Major, Sanitary Corps, U. S. A.*

When, on the 4th of August, 1914, England declared war on Germany it was a foregone conclusion that a blockade would at once be established, and a question thrust itself upon everyone who had any knowledge of German economic life: Could Germany hold out through a long war if cut off from her considerable imports of food and fodder? The question of a nation's food supply during war is such a problem that for its full appreciation and solution the politician, the political economist, the statistician, the physiologist, the farmer, the geologist, and the housewife must each be called upon to contribute his or her share of knowledge. With the question clearly before them, the German authorities at once proceeded in a typically German manner to attack the problem. The result was a large committee, which eventually, under the leadership of Eltzbacher, produced a volume called "Die deutsche Volksernährung und die englische Aushungerungsplan." This volume was Germany's answer to the blockade.

The volume sets out to show the German food requirements, first per capita, and then translates this into national needs of millions of tons of protein and milliards of calories. The national consumption is analyzed into home produced and imported, accurate estimates and percentages calculated as to protein and calories coming from abroad, and finally the work

points out that the German nation can hold out indefinitely, provided the advice given is followed. There is every reason to believe that the book is a serious attempt to solve the most difficult of all the questions which the Germans faced, and had the German Government heeded to a greater extent the ideas advanced there seems to be good reason for feeling that the "Aushungerungs" plan would have failed.

The essential data in the memoir are to be found in the tables, which are attached, a study of which will help greatly in an appreciation of the food problem in Germany. Dr. Waller, of the University of London, in his preface to the English translation of the volume, has summarized these tables as follows:

Germany used of protein in 1912-1913 .....	2,261,900 tons.
Germany can live upon.....	1,605,000 tons.
Home resources normally produce.....	1,554,000 tons.
Home resources can produce.....	2,022,800 tons.

This table, translated into per capita per day consumption, a form more comprehensible to the average person reads:

Protein consumption, 1912-1913.....	93.0 grams.
Minimum physiological requirement.....	64.0 grams.
Home resources normally produce.....	62.5 grams.
Home resources can produce.....	81.5 grams.

This table, as will be noted, is based on a per capita per day basis, and not on a per *man* basis. For all ordinary purposes the total population (men, women, children) multiplied by 0.80 will give the *man* population. The Interallied Scientific Commission of Food sets down the following factors as being official in the countries named for the calculation of man population:

For the United States...0.84	For France .....	0.85
For the United Kingdom..0.835	For Italy .....	0.826

The German factor, as calculated by the Germans, varies between 0.7625 and 0.8085, in either case being a much lower figure than any quoted above, due to the larger child population of Germany. On the per *man* per day basis the German data show that:

Protein consumption 1912-1913 was.....	116 grams.
Minimum physiological requirement is...	80 grams.
Home resources normally produce.....	78 grams.
Home resources can produce.....	102 grams.

It will be noted that the protein requirement is set rather low, not only as regards the German consumer, but as regards the scientific consideration involved. This will be referred to later.

The total calories required received the same careful attention and the data, scientific and statistical, resulted in the following tables:

Calories consumed, 1913-1914.....	90.42 billions. <sup>1</sup>
Physiological requirements .....	56.75 billions.
Normal home production.....	57.68 billions.
Home resources can produce.....	81.25 billions.

This table translated into daily consumption reads:

	Per man	Per capita
Calories consumed, 1913-1914.....	4779	3642
Physiological requirements .....	3000	2287
Normal home production.....	3577	2727
Home resources can produce.....	4295	3274

This showing in relation to calories is much more promising than the protein showing.

The amount of food imported prior to the war is shown in the following paragraph from the German Memoir, page 74, English translation:

Our total consumption of all foodstuffs before the war amounted to 2,261,900 tons of protein, 2,581,000 tons of fat, 12,913,000 tons of carbohydrates, and 88,649 million calories came from abroad. We therefore had to thank the foreigner for 26 per cent of protein and 20 per cent of calories.<sup>2</sup>

From a study of the above figures the deficit is obvious. However, on the total nutrients there is a deficit only in relation to the standards of consumption; the real needs are more than met. In the case of protein there is a deficit, not only in relation to consumption, but in relation to needs, and that on the basis of the protein need which it appears is set too low. One of the causes of the especial shortage in protein is to be found in the lack of foreign fodder, it being impossible for Germany to trade her protein-free sugar for protein-building foods.

<sup>1</sup> The German milliard = 1000 millions or 1,000,000,000. The German billion = 1 million millions or 1,000,000,000,000.

<sup>2</sup> See attached table, Number I (Page 75, Eng. Tr.).

Such, very briefly, was the situation in 1915 as seen through the eyes of the best men in Germany. One must look further and see how it was planned to meet the deficit caused by the blockade and then, to get a picture of the whole, must consider what happened as the war progressed in order to appreciate fully the condition found in Germany in January, 1919.

The problem which the German nation faced was one of making its income meet its needs. Inasmuch as consumption had been in excess of needs it became necessary to reduce the consumption, which, if done wisely, would result in the solution of the problem as it related to calories, for the normal home production of total food value was greater than the national need. But to meet the protein deficit, the country normally producing only 97 per cent of the low estimated needs, was a serious problem. Not only must the 3 per cent be overcome, but enough more produced to allow for the inevitable losses occurring in handling. From physiological standpoint the protein deficit was further complicated by the fact that the body has no protein reserves, but lives a hand-to-mouth existence in this relation. The fat and small carbohydrate reserves, when supplemented by even an inadequate diet, can be made to last for surprisingly long periods. Long before these reserves are exhausted there is a genuine call for protein.

One of the first procedures advised was an immediate reduction of the live stock, and especially of the hog. Stock consume mostly vegetable foods, convert it into meat and fats which are then food for humans. Certain animals can eat the foods which man cannot consume, *e.g.*, cattle and sheep will maintain themselves on pasture and straw or hay, foods entirely useless to man, and these animals will convert this inedible material into a food useful to man, either as milk or as meat. On the other hand, the hog is not an animal that can live in such a way. A hog must be fed upon materials which will also make human food. The hog question is clearly shown in the following statement of a hog's converting efficiency:

Food required to fatten...Protein, 45 kg. Calories, 1,327,000
Fat hog produces.....Protein, 11 kg. Calories, 607,750

Therefore, in the fattening process we are able to recover from the hog only 24.4 per cent of the protein given and only 44.3 per cent of the calories supplied and there is good reason to believe these figures are high. Unless the hog is going to be fed entirely from the foods not edible by humans it would be wiser to eliminate him. This problem of the hog as a competitor for human food received a great deal of attention in Germany through the war, and the fact that in

1914 there were 26,000,000 hogs, and in
1919 there were 8,000,000 hogs

shows that beyond a doubt the situation had become serious. This great reduction in the stocks of pigs was not, however, the result of the advice given to reduce the number. Had the reduction been carried out scientifically, the meat carefully cured and stored, the country at large would have fared better. As it was, with every change in crop outlook the attitude towards the hog changed. To have ordered the entire

nation to slaughter all the hogs would have been an impossible measure, so the situation took a natural course. When it looked as if there was going to be a shortage of food for the hog, the people began to slaughter, and for a period there was a great plenty of meat; then followed a period when there was less, and this alternation kept up until the hog stock of Germany became too low to permit of any further reduction. It is interesting to note that each successive period showed a smaller and smaller meat supply. The German policy in relation to the increase of the protein supply may be quite simply stated: "Do not feed an animal grain which you could eat because you must allow the animal a 75 per cent profit. Eat the vegetable protein yourself and save the animal profit."

The solution of the problem lies in a broadening of the vegetable basis of the human food supply, and a simultaneous slight contraction of its animal basis. A general principle may be deduced that when the vegetable basis of the human food supply suffers contraction, the amount of vegetable food for direct human consumption must be immediately increased. If a sufficient increase cannot be effected because the food of animals has been composed largely of grass and hay, which are not suitable for human food, then part of the meadowland should be converted into ploughland so that the requisite vegetable calories may be secured for human nourishment by increased cultivation of grain and potatoes. In any case it is a completely mistaken policy, when the general vegetable basis of the food supply has undergone contraction, to reduce the direct human consumption of vegetable foodstuffs for the sake of producing animal foodstuffs. If a workman, on finding that the amount of vegetable calories available daily has been reduced from 7000 to 5600, seeks to reduce his consumption of animal calories from 2000 to 1000 in order that he may have 4000 calories for conversion into animal food, he will obtain from such conversion only 920 calories, and his total daily food supply will therefore amount to 1920 calories; this is absolutely insufficient, and he will not be able to continue his daily work without using up his physical capital, losing heavily in weight, and eventually falling into disease. By raising his direct consumption of vegetable food to 2500 calories per day, on the other hand, he will be able to obtain the same number of calories as before, and even a little more. But this method, of course, can only be effectively applied if the cattle stocks of the country are reduced to such an amount as can be properly fed with the diminished supply of fodder. Otherwise the vegetable calories used for fodder will be partly or wholly wasted, instead of undergoing conversion into their full equivalent in animal calories.

A practical illustration will make this clear. Suppose there are two families, A and B, which are exactly similar in circumstances, but pursue opposite food policies during the war. Each of these families consists of five members, and possesses a plot of land which yields annually 2500 pounds of bread grain and 7000 pounds of potatoes; each family keeps a goat, which lives on grass, hay, and kitchen waste, together with two pigs every year, which are brought each to a slaughter weight

of 300 pounds. The grain and potatoes grown by each family are not by themselves sufficient for the feeding of the family and the fattening of the pigs, and each family therefore has to buy 500 pounds of bread grain and 1500 pounds of potatoes every year; so that altogether each family has 3000 pounds of bread grain and 8500 pounds of potatoes at its disposal. Each family consumes 1500 pounds of bread grain and 2500 pounds of potatoes directly, and uses the remaining 1500 pounds of grain and 6000 pounds of potatoes for the fattening of the two pigs to a slaughter weight of 300 pounds.

The outbreak of the war makes the purchase of grain and potatoes impossible, and each family is compelled to rely exclusively upon its own production of 2500 pounds of grain and 7000 pounds of potatoes. Family A resolves to keep only one pig; this one pig is fed, as in time of peace, with 750 pounds of grain and 3000 pounds of potatoes, and brought in this way to a slaughter weight of 300 pounds as before. For its own direct consumption family A has therefore 1750 pounds of grain instead of 1500 pounds as previously, and 4000 pounds of potatoes instead of 2500 pounds. These quantities are more than sufficient, so that a part of them can be supplied as additional fodder to the pig, which is thereby further fattened to a slaughter weight of 350 pounds. Family A by this method secures a more ample supply of vegetable food than in time of peace, together with an adequate, though diminished, supply of animal food.

Family B pursues an opposite policy. It resolves to maintain two pigs, as in time of peace, and to divide the deficiency of 20 per cent equally between men and pigs. The hard working members of the family lose weight, and the pigs do not grow fat. The fodder supplied to them is wasted for the most part in their mere maintenance, and they put on very little meat. When the fattening period is over and the appointed supply of fodder completely consumed, it is found that the slaughter weight of each pig is only 150 pounds. Family B therefore has only 300 pounds of meat as against 350 pounds secured by family A; and, moreover, the quality of this meat is very much inferior to the quality of that secured by family A. One kilo of lean meat yields only 1000 to 1500 calories, whereas 1 kilo of fat pork yields 4500 and pork fat ("speck") as much as 7000 calories per kilo. The single pig maintained by family A has therefore at least three times as much nutritive value as the two pigs maintained by family B.

The father of family B does not perceive that his policy has been radically wrong. Disputes have arisen in the family because the housewife has occasionally given a handful more potatoes to the hungry pigs or a handful more bread to the hungry sons than was provided for in the scheme of rationing. The father considers that such irregularities are the real cause of his failure, and resolves therefore to pursue the same food supply policy in the coming as in the past year, but to enforce it with more energy and strictness. The energetic prosecution of a mistaken policy does no good; the previous difficulties remain and the discontent in the family increases.

Germany has pursued the same policy as family B, and all her food supply difficulties arise from this fundamental fact.

She has aimed at maintaining her large stock of cattle undiminished through the war, despite the stoppage of concentrated fodder imports; whereas she ought to have adjusted the stocks of cattle to the available fodder supplies by means of a scientific reduction. As a matter of fact, the stocks have been allowed to attain dimensions never reached in time of peace. They numbered 21,828,783 head on June 1, 1917, as against 20,994,341 head on December 1, 1913, although it is true that the number of cows shows some diminution. At the beginning of the war an attempt was also made to maintain the pig stocks at the level of peace time, and although reduction was afterwards undertaken, it has not been sufficient to allow proper feeding of the stocks which have been kept. The authorities have worked directly for the maintenance of excessive cattle and pig stocks by means of slaughter prohibitions, excessive promotion of breeding, promises of official supplies of concentrated fodder, and reduction of meat rations. The result is that large quantities of vegetable food and fodder stuffs have been wasted in the mere maintenance of cattle and pigs, without any production of meat or fat. The ill-fed cattle have deteriorated considerably in quality, and there is less meat, fat, and milk for the public than would have been obtained from the same quantity of fodder if fed to a smaller number of cattle. Not only so, but the bread and potato rations for human consumption have been reduced in order to make grain and potatoes available for the maintenance of cattle.

Economy in bread and potatoes has been preached, although in reality true food economy would require the fullest possible direct human consumption of bread and potatoes up to the physiological point of satiation. Economy in the use of bread and potatoes, in order to use them as fodder, means an enormous waste of food supplies. This waste must be estimated at many million tons yearly, since not only are foodstuffs withdrawn from direct human consumption, but fodderstuffs, unsuitable for human food (hay, roots, beet-slices, etc.), are wasted in the maintenance of cattle, instead of being profitably used for their fattening. The result is that Germany, like family B, suffers from shortage of vegetable and animal food alike. If she had pursued the same policy as family A, and had scientifically reduced her cattle stocks, she would now have an ample supply of vegetable food and much more animal food than she actually has. Nor would her cattle stocks be in any serious danger. In Germany, unlike England, the vegetable basis of the food supply is broad enough to allow under all the circumstances not only an ample supply of vegetable food to the public, but also the proper fattening of a considerable part of her cattle stocks, without any import being required. The policy pursued by the German authorities has considerably accentuated instead of counteracting the effect of the British blockade. A complete break must be made with this mistaken policy. The authorities must be brought to see that the present is no time for the hoarding of cattle with a view to the *post bellum* period.

Finally, there were powerful political reasons for an immediate comprehensive improvement of food conditions. The widespread discontent among the German people is due mainly

to the dislocation of the food supply, and will disappear as soon as this dislocation is remedied.<sup>3</sup>

But for all the elaborate plans, in spite of the continual assurances that they were getting enough, in spite of the rigid food control and food rationing, something was wrong. On paper, at least, everyone was getting all the calories he needed, but he was hungry all the time. Throughout 1915 things ran smoothly, due to the popularity of the war, the patriotism of the people and their perfect confidence in the outcome. Then came the poor crops of 1916, and from that time on things have gone from bad to worse. A typical example is shown in the attached chart which gives by six-month periods from July 1, 1916, to January 1, 1919, the complete figures for the food allowed for one person by the prescribed ration. The second part of the chart contains a résumé showing the content of the ration, by periods, in fat, protein, and carbohydrate, and its caloric value. A careful study of these figures will show something of the seriousness of the situation. With an average caloric value of about 1500, the ration probably represents less than 1000 calories of value to the body because of the low digestibility of most of the foods. The bread as supplied, in the course of digestion loses 40.3 per cent of the nitrogen and 14.8 per cent of the total calories, and the "Steckrüben" supplied so freely as a potato substitute in 1916-1917 loses 66 per cent of the nitrogen content and 22 per cent of the caloric value. Nor was it possible to improve the diet, because the only foods available were the vegetables of a similar character, with high cellulose content. There was, to be sure, a great deal of food which could always be purchased at high prices through illegal methods, but this food never got into the hands of the poor, the people who needed it most.

The policy of rationing the food caused a great deal of trouble. Any attempt to bring a large group of people under one diet will always result in grave inequalities. In his report of December, 1917, Rubner refers to this situation with some bitterness. He said:

The more thoroughly we consider to-day the conditions of national nourishment in their effects upon health, the more the conclusion is forced upon us that the blockade and embargo compel us to get along with our own food products, but that the real basis of the injurious effects of the diet to be traced lies merely in the distribution of the food, which works disadvantageously for individual sections of the nation and certain groups of persons. In the very beginning we pointed out that the distribution between city and country has turned out to the disadvantage of the city. It was not necessary to change the composition of the diet of the rural districts and it has in many sections, where the diet was formerly very poor in meat, become richer in meat, due to the establishment of the Imperial Meat Bureau. . . . It is, however, clear that the very principle of economy itself is violated by any system of rationing, and that such a system in and of itself, if it is made as simple as possible, comes into conflict with the attempt to supply the population with proper nourishment. The amount of nourishment required depends upon the mass of a human being's body and its functions, which vary in both large and small cities according to the climate, clothing, season of the year, calling, habits, sex, age, psychic differences, etc., and which again vary for

<sup>3</sup> G. Oetelshofen: Kölnische Zeitung, October 14, 1917.

each individual with every day of his life. The natural amount of nourishment taken in is in every case regulated by requirements, as noted by sensations of hunger and of repletion. In individual cases these sensations, like every other function, may vary from the normal, being either decreased or increased in an unhealthy manner. The nourishment desired is closely adapted to the nourishment required, hence the conditions of balance often maintained for years in an adult. To-day, however, we have come to a rationing of foods to so large an extent that the ration alone gives the bulk of the nourishment, and permits the free purchase of other things only to a limited and inadequate extent. The present plan attempts to nourish with little variation, infants, children, pregnant women, nursing mothers, persons working fairly hard, and persons engaged in the hardest kinds of labor, with an amount uniform for all, with the same kind of food for each class, and through very limited supplies given out at very short intervals and throughout the entire Empire. Such a nation-wide system of food distribution as compared with self-regulation does not lead to economizing, but to an excessive consumption of supplies.

The food system behind the front recognizes no social distinctions according to needs, no individual prerogatives, neither the particular requirements of men and women nor the trade distinction between quite heterogeneous elements, and in the case of adults; no distinction of age. The classification into workers and non-workers takes from the latter every chance of bettering their condition. The amount of food allowed by a food ticket is purely a mathematical quantity, of interest as such when considered from the standpoint of national economy or physiology, but which in its practical application works a grave injustice. It is a correct estimate, provided the holder possesses the average weight of the nation; for those underweight it is too much, for those overweight it is too little, nourishment. Families with young children have a better chance of evening up inequalities than a family with grown children, while elderly people who usually live alone fare very badly. The artificial distribution as carried on at present can never provide proper national nourishment."

There is a very definite causal relationship between the inadequacy of the rationing system as worked out in Germany and the government policy of price fixing. In normal régime, where the laws of economics, competition, etc., are allowed free play, all prices seek a level that is just and fairly constant. In setting the maximum prices for farm produce the government had in mind only the proper alimentation of the nation. Due to the severe lines of the ticket system for procuring food, there arose a demand in certain places for certain foods, and this demand in turn led to the offering of greater prices than the prescribed maximum, and out of this situation, due partly to the low maximum set and partly to the weaknesses of the rationing system, developed the entire system of "Schleich-handel." The government made one grave mistake. The price of farm produce was set, but no effort was made to regulate the price of labor, the price of machinery, nor the price of fertilizers. The farmer saw men going to the munitions factories and receiving a much larger wage than ever before paid in Germany; in addition certain rich men were making huge war profits, these things leaving the farmer able to collect only his rather low maximum price, due to the price fixing policy. The only natural outcome was the extensive illegal dealing which grew to large proportions before the end of the war. This fact accounts for a great deal of the shortage in such items as butter, fats, milk and meat.

<sup>a</sup> Unpublished report of Rubner, December 20, 1917.

The ultimate outcome of the entire situation was a large number of grave discrepancies in the national nutrition, wherein it was almost impossible for the poor to get proper food, while the rich had all they wanted. The actual diet allowed by ticket was not enough for human subsistence. A number of German scientists worked on this very problem—Rubner, Neumann, Bach, and Fr. Müller. Neumann,<sup>b</sup> working in Bonn, has supplied the writer with a vast amount of extremely valuable data and charts. In Bonn, from July 1, 1916, to July 1, 1917, the average value of the foods supplied on ticket was:

Protein .....	41.00 grams.
Fat .....	20.00 grams.
Carbohydrate ..	280.00 grams.
Calories .....	1510.00

Nor was Bonn the only city to find that the ticketed supply would not meet human requirements. In the summer of 1916 the supply was:

In Berlin .....	{ Protein .... 36.3 grams. Calories .... 1312.0 }	{ Loewy.)
In Wiesbaden .....	{ Protein .... 43.6 grams. Calories .... 1547.0 }	{ Arnold.)
In Munich .....	{ Protein .... 45.9 grams. Calories .... 1709.0 }	{ Köhler.)

While living on the rationed foods for a period of seven months Dr. Neumann records total weight loss of 37 pounds, or 18.5 kilograms, the beginning weight being 76.2 kilograms and the end weight being 57.6 kilograms. During the period of the observations Dr. Neumann was engaged in active work at the university, and during the last two months went into the fields and did the work of a farmer in addition to evening work at the university.<sup>c</sup>

This condition of loss of weight has been true all over Germany. If the average weight loss has been to a degree approximating that recorded above, then it is easy to figure what the national loss has been, not only of weight, but along the lines of efficiency and ability to work. There is no reason to believe that the average loss per man was anywhere near the figure set by Neumann, for the reason that a great deal of food moved through channels other than the official ones; probably between 25 per cent and 33 per cent of all food in Germany was sold through "Schleich-handel." This fact enters into all considerations of the nutrition of the masses during the war, and must always be borne in mind in following any discussion of the food. What the German was allowed on ticket and what he really managed to obtain were quite different things, probably spelling the difference between a starvation diet and a living one.

Taking into consideration the low digestibility of the foods supplied it cannot be assumed that the rationed foods actually delivered to the body more than 1000 to 1100 calories daily. It needs no scientific proof to show that a hungry person needs more than 1000 calories daily, to satisfy his needs.

<sup>a</sup> Die Kriegernährung in Bonn im Winter 1916/17, u. s. w. von R. O. Neumann.

<sup>b</sup> See Table IV (Neumann).

From a great deal of experimental work it is well known that the average person requires between 30 and 32 calories per kilogram of body weight, this when he remains quietly in a room and does no moving about. This figure is known as basal metabolism, and any estimates of a person's food needs must take this figure as a basis to which all others are added. Hence a man weighing 60 kilograms will need for his basal requirements about 1860 calories daily delivered to the body. If he were supplied with foods of the best quality, the gross need would be for 2065 calories in order that the losses of digestion might be compensated. With the rationed diet there is no doubt but that the Germans, as a nation, lost considerable weight. When a person begins to lose weight the loss consists of those things lacking in the diet, either from the fat layer or protein, probably both if the insufficient diet is maintained for sufficient time. By these losses the human being reduces the mass of the body, arriving at a new scale of weight and therefore a new level of nutrition. But this attempt at adaptation can only proceed to a certain limit; from animal experiments and observations on humans it is known that starvation ensues when the body weight which was previously normal reaches a half.

The data furnished by Neumann in his experiment upon himself throw some interesting light upon the problem of body requirements and the relation to weight losses. Neumann lived for seven months on the following ration:

Protein .....	45.00 grams daily.
Fat .....	18.90 grams daily.
Carbohydrate .....	236.00 grams daily.
Calories .....	1546.00 daily.

During the period of the experiment he lost 18.5 kilograms or 24.4 per cent of his body weight. Towards the end of the experiment the rate of loss had become less rapid. From this it can be reasoned that the calories supplied were only 75 per cent of the amount necessary to maintain the body, that to have done the same work and to have held the beginning weight the body should have had about 2060 calories. Unfortunately, we have no data relating to the nitrogen losses during this work.

The question of the nitrogen metabolism is of especial interest since the lack of protein was, throughout the war, one of the distinguishing features of the diet. The much discussed question concerning the amount of protein necessary for a human was again revived in Germany, this time with a peculiarly human interest. In discussing this point at a conference in January, 1919, Rubner said that the grand experiment was far superior to 70 million rabbits. Bach,<sup>1</sup> working in Bonn, found that a nitrogen balance could be maintained on a protein turn-over of 0.92 gram per kilogram of body weight. This figure was the result of a long series of experiments on himself and four others, all living on the rationed diet. For a man of 70 kilograms weight this calculates to a protein need of 64.4 grams daily, a figure strikingly near that set by Chittenden.<sup>2</sup> However, the consensus of opinion as

voiced by the German scientists is that as soon as possible the people will get back to a higher level of protein metabolism. The war diet was forced upon the people by want, best illustrated by the loss of weight recorded from all parts of Germany. In a conference Rubner referred to the need of protein as follows: "No human being can perform work if the muscles are insufficient. One fact is very interesting, *viz.*, that the loss of protein, due to the very small quantity of this substance contained in the alimentation of the people, can follow a steady course and may continue for quite a length of time before the effects become noticeable. In order to bring the population back to its old standard small amounts of protein are of no avail; protein must be given in increasing doses. Food containing protein will be able to rebuild the nation as a whole." And through all the German writings runs a rather hazy idea; no one is willing to predict, yet all express, a grave fear for the future results.

Another interesting fact has been noticed, for some years known in relation to animals, but owing to the lack of opportunity, not followed up in the case of humans. In animals it has been found that, after starvation or undernourishment has been allowed to proceed beyond a certain point, it then becomes increasingly difficult for the animal to maintain a protein balance even when fed relatively enormous amounts. This fact has been reported in many instances in Germany in which persons who have lost weight almost to the limit are frequently unable to establish a balance even when fed as much as 100 grams of protein daily.

The low protein diet has led to some other results. It has often been noted that many persons suffering from malnutrition were anemic. This would lead to the belief that the body, in order to prevent its own death, can set great limitations as regards the renewing of organs, above all else the formation of new blood, the reconstruction of tissues, and the healing of wounds. This is most strikingly shown in the great number of reports which have referred to a common condition found in women, suppression of menstruation for long periods, and among men to the less frequent report of testicular atrophy and a greatly decreased sexual libido. Perhaps there is some connection, after all, between the rapidly declining birth-rate in Germany and the low protein diet.

In addition to an actual loss of weight most of the German observers point to other results, loss of efficiency, morale, etc. They point to widespread slowing up of national industry, loss of endurance, the ease with which persons become fatigued, a great tendency to forget, and among professional people a loss of initiative. Most of these results are not physical but mental; in fact the entire German nation to-day is undergoing great psychological changes, unrest, riot, and revolution being rampant. That this is solely the effect of empty stomachs and hunger pangs, as the German writers would have us believe, hardly seems logical, but that hunger has played its part goes without saying.

The question of the bread supplied the German population is worth some consideration.<sup>3</sup> In peace time the bread fur-

<sup>1</sup> Bach: Berliner klin. Wochenschr., 1919, No. 6.

<sup>2</sup> Chittenden: Physiological Economy in Nutrition. 475 pp.

<sup>3</sup> Rubner: Report to the Public Health Department, 1917.

nished more than one-third of all the calories in the average diet. Of every 100 calories there were:

Peace times, in bread.....	36.9 calories.
Fall, 1917, in bread.....	51.2 calories.

In fact, bread and potatoes constituted the bulk of the ration and it was not everywhere that even these articles were fully supplied. In order to combat the increasing grain shortages the flours were ground out to 94 per cent. This was done in order to supply the people with bulk. It is a question whether the practice did in the end result in economy or loss of good food materials. The chief difference between a low percentage flour and a high percentage flour is the cellulose content. The grain, consisting of the germ, the endosperm or the kernel, and the bran, the outer envelope, consisting of cellulose and mineral salts, shows the following approximate proportions of the parts:

Germ .....	1½ per cent.
Endosperm .....	85 per cent.
Bran .....	13½ per cent.

In milling, the process tends to grind out, as far as possible, the cellulose. The cellulose is the chief constituent which enters into the bulkiness of bread.

Two factors largely determine the digestibility and absorption of foods in the process of digestion: The first is the bulk; the second is the cellulose content. The bulkiness of vegetable food interferes with digestion in two ways. The digestive juices have difficulty in penetrating such a mass so that the conversion of the constituents into products capable of absorption is apt to be quite inefficiently carried out, and the large mass has a tendency to hasten the intestinal peristalsis, the contents of the gut are thus pushed forward too rapidly; and even were digestion more complete, the absorption could not keep pace with the food movement. In this connection it is interesting to note that the herbivorous animals have relatively much larger intestinal tracts than the carnivorous animals. Hausemann, working with the Russians, confirmed older data to the effect that the Russian had a longer intestine than most other of the Europeans, not in the sense of a race characteristic, but as an adaptation to the diet which was hard to digest, such a diet as the Russians live upon.

The presence of cellulose is the second great factor in the retardation of digestion and absorption. In the case of meat, the nutritive constituents are held in tubes, composed of gelatin, which readily digest; in the case of vegetables, the starch is contained in cubical compartments with walls of cellulose. Cellulose is a carbohydrate, belongs to the class of polysaccharides, and is especially characterized by its extraordinary insolubility. From this it can be seen that the presence of cellulose influences digestion and absorption in several ways. It not only has little or no food value of itself, but it prevents the access of digestive juices to the mass of food in the stomach, and it prevents the juices penetrating to the individual starch cells. Further, by increasing the mass to such an extent it has a tendency to stimulate the intestinal movements and hasten the progress of the food.

Romberg has worked out the following table of composition and percentage loss in digestion of protein in four grades of rye flour. Grade No. 1 was made from the endosperm only, and was pure white; grades No. 2 and 3 had increasing quantities of bran included; while grade No. 4 was made from the whole grain.

	Protein content Per cent	Loss in digestion Per cent	Protein absorbed Per cent
No. 1.....	7.43	22.00	5.80
No. 2.....	11.59	28.60	8.28
No. 3.....	17.28	30.50	12.01
No. 4.....	16.84	43.00	9.60

As far as the protein content is concerned, mixture No. 3 is the most efficient as a human food. Unfortunately, the author does not state what percentage of milling each grade represents, but it is clear that the whole meal bread is not so good as the other grades.<sup>10</sup>

It is evident that in the milling of flours there comes a point in the grinding out where the law of diminishing returns begins to play; that is, there is a percentage at which the milled flour is the most efficient food deliverer. That the flour must not be milled to too high a percentage is evident, for the great cellulose content will not only hamper the digestion of the protein, but will interfere with the digestion of the carbohydrate. In the case of the German flours during the war, especially when the one great problem of the diet was protein, the mistake of grinding out to 94 per cent is quite obvious. Not only was the bread actually less efficient as a food, but by milling to a lower percentage the bran would have been used as fodder, thus putting it to a useful purpose instead of allowing humans to eat it with no good to them; rather it did actual harm, in that it caused, indirectly, a portion of the available protein to be lost.

These facts were all well known to the German scientists; in fact, they advised that rye be ground out to 70 per cent only, but here again the authorities could not or would not follow the advice given. To have ground to 70 per cent instead of 94 per cent would have meant a loss of about 20 per cent of the bulk of the flour, and when it was a case of filling stomachs little attention could be paid to the quality. When one realizes that the Germans had been importing annually 2,263,654 tons of cereals, about 30 per cent of their total consumption, the necessity of increasing the quantity is apparent. Nor did the lowering of the quality of the flours stop at the milling process, often it contained a number of foreign substances, wood pulp, weed seeds, straw, etc.

All this seriously affected the fodder situation, which in turn had a direct influence on the milk, meat, and fat supply. Attempts to increase production were not successful because labor was extremely scarce, fertilizers could not be had, and the number of animals for draught purposes, due to the shortage of fodder, was materially decreased.

As already stated there was a great deal of dissatisfaction created throughout all Germany by the evident inequalities

<sup>10</sup> Romberg: Arch. für Hygiene, 1897, XXVIII, 24. See also Table III.

and unfairness of the system of rationing. So there stand two clear issues in relation to the problem of bread: (1) Shall it be rationed, and (2) what percentage flour is the most efficient as human food? In this connection it is worth while to see what action was taken by the British. It must be borne in mind that the problems presented in England were of a different nature than those in Germany. Germany was forced to live upon what she could produce within her own borders plus the small amounts she could get from contiguous nations or occupied territories. England, on the other hand, had to depend to a large extent on the importation of food materials. Hence any form of control in Germany had to extend to the producer, and had a number of evils as well as a host of difficulties. For the state to pre-determine the time and amount which the farmer must deliver involves the risk of serious miscalculations and much irritating interference with the farmer's operations. At the same time, the German system of paying a higher price for grain which was delivered in the later months ended in the grain being held for the advanced price. In either case the government had to deal with a large number of individuals, each one a producer. Just what would have been the effect of allowing bread to move freely without ticket is hard to guess. In England there never was a limit on the sale of bread. To rather encourage its sale the government bought large quantities of breadstuffs and put these on the market at low prices. Price and nutritional value considered, bread is the cheapest food obtainable in normal times, and even when prices are advancing, bread still remains the cheapest food. This fact, and the fact that people will tend to eat more bread as prices rise is shown in the following:

Peace time bread consumption... .5% lbs. per capita per week.  
War time consumption.....10 to 14 lbs. per capita per week.

It will be seen that in pre-war days the workman, then able to fill in his ration with other types of food, ate only  $5\frac{1}{4}$  pounds of bread per week, but when the prices began to rise these other foods, eggs, meat, cheese, etc., increased so rapidly in price that the poor had to depend more and more on bread, because it still remained the cheapest available food.

But all of this Germany was unable to do. The reason is very clear, she did not have enough flour with which to make an unlimited supply of bread, consequently she had to resort to the very system she did. It is in fact more or less waste of time trying to compare the systems in force in the two countries, because the systems followed were the outgrowth of the conditions which existed, and the conditions were the result of a number of causes.

In the past, the science of nutrition, in treating the subject of the body needs of the three classes of foodstuffs, has devoted a great deal of attention to the caloric needs of the body, to the minimum protein requirement, and over this very question of protein has been waged a merry war for years; but it took the war with its subsequent world food shortage to bring into prominence the question of fats. With an individual or a nation living on the average mixed diet there never is a question of protein minimum or maximum, unless it is purely an academic one. In the case of the carbohydrate, it is well

known that a certain amount is necessary, sugar being the form in which the body finally deals with this food. If carbohydrates are lacking, then it is possible for the body to split off the oxy-fatty acids which result from the de-aminization of the amino acids of the protein. Data regarding the necessity of fats in the diet are not on record, or are very scanty. Generally, dieticians have assumed that fat and carbohydrate are isodynamically convertible; the fattening of stock from carbohydrate is well known. The isodynamy in the case of carbohydrate is very limited, probably the glycerin radical of the fat molecule offering the basis for carbohydrate synthesis.

That the body needs protein and carbohydrate is known. Is there a similar limit in the case of fats? Inasmuch as the body has the power of converting sugar into fat the physiological needs of the cells for an outside supply of fat appears to be unproven, at least from the viewpoint of nutrition and chemistry. However, there are a number of other considerations to bear in mind. For the past three years the German nation has been on an exceedingly low fat diet, in some cases as little as 30 grams per week per person. The first demand made was for fats. If fats cannot be proven by science to be necessary, at least in the mind of the people fat holds a place of high esteem. There probably is some real reason back of this craving for fats, more than the people themselves know. It is known that the fats are rather slowly digested. Further in the preparation of foods, fats play a large part in the palatability of the dish as it goes to the table. Food coated with hot fat is more palatable and therefore more satisfying, but the fat has another and a more important rôle to play. The digestion of that food is retarded quite considerably, the sense of fullness remains much longer and hunger pangs are not so apt to develop. The Germans had for a long time been eating foods prepared without fats; as a consequence, the methods of preparation were very limited, and lacking the protective fat covering the food was rapidly digested with a consequent sense of hunger rapidly developing. In this case the fats were playing a double rôle, physiological and psychological.

Then, too, there have developed certain diseases both in England and Germany, chief among which is a form of generalized edema, more commonly called war edema. In England this disease followed closely on the development of a fat shortage and cases cleared up rapidly when fat in sufficient quantity was added to the diet. In Germany there was a great deal of the same disease and the same cures were noted. However, the German medical men state that they found it was not necessary to give fats, but that any complete change of diet would clear up the edema.

Living on such a diet as the Germans did for so long must have led in many cases to undue distention of the intestinal tract. The diet was extremely bulky in relation to its heat value. Perhaps the demand for fats comes from this fact as well as those just mentioned. Fat is the most concentrated food we have. It will yield 9.3 calories per gram as compared with protein or carbohydrate, both of which yield only 4.1 calories per gram. The addition of a small amount of fat to

the diet would have added a large increase in caloric value with comparatively little bulk, which would have gone towards relieving the packing of the digestive tract with large amounts of highly indigestible foods.

In the digestive tract the fats are less liable to fermentation than the carbohydrates. The overloading of the intestines with carbohydrates will lead to meteorism, a complaint very common among the Germans, and will lead to more or less chronic forms of intestinal irritation.

In general, then, we have three very good reasons for believing that fats are really quite essential to proper nutrition: (1) They retard digestion and so ward off hunger pangs; (2) they are a highly concentrated form of food; and (3) they are less liable to cause meteorism in the process of digestion.<sup>11</sup>

In summing up the entire situation it will be well to refer to certain memoranda and extracts from reports in order that the entire situation will be seen. On April 8, 1919, the writer prepared the following memorandum on the breakdown of the German food control:

As compared with England, Germany had far the more difficult problem. In England, where most of the food was imported, a barrier at the dock was sufficient; while in Germany, with all imports cut off, it was necessary to control every individual producer. To do this successfully required the full and honest coöperation of every farmer. This the government had during the early days of the war, but later, as food shortages became more acute and prospects of a victory became more distant, the control of the farmer became less and less efficient. The lack of coöperation by the farmer was further augmented by the government's policy of price fixing of foodstuffs, while the price of labor, machinery, animals, and fertilizers continued to soar. In addition, taxes were greatly increased, war loans were being floated, of which the farmer was expected to bear his share. To meet this increased cost of living the farmer resorted to a number of illegal practices, chiefly "Schleich-handel," and as the practice spread the control became weaker and weaker until in the end probably the control covered as little as one-half the total production.

Germany's attempt to ration the nation caused considerable trouble. It caused grave discrepancies in the food supplied. On paper, every man shared alike; in reality, certain people were much better off than others. In the first place, as pointed out by Rubner, it is impossible to arrange a system of rationing food which will meet every individual's needs, assuming an unlimited supply. But, considering the situation in Germany, where the supply was distinctly limited, then a problem in rationing becomes extremely serious. Families with many children were better off than families with no children; hospitals, prisons, and asylums fared badly. Every consideration was given to the war industry worker, while the hard mental worker suffered. No consideration was given to the dietary habits of various portions of the Empire, no consideration was given to the relative needs of city and country. In the case of the city and country it must be borne in mind that the urban population in Germany was, relatively speaking, a meat-eating population, while the rural population subsisted largely on vegetables and bread. When the one level ration went into effect it resulted in a relative increase in the rural diet, whereby the farmer was able to obtain more meat than in peace times, but he obtained this meat at the expense of the city dweller. And due to the fact that the farmer was the producer of grains, he was able to maintain his former standards of living regarding bread and vegetables. So, as regards city and country, the country

had every advantage at the expense of the city, from a dietetic standpoint, while the city had all the advantage from a financial standpoint. "Schleich-handel" was the great adjuster between these conditions. The fact that health conditions, changes for the worse, are more in evidence in the cities lies at least partly in this situation. The situation in Germany has again proven the truth of an old statement regarding the feeding of a nation, that any attempt to control the diet of a large group of people would always be a failure.

The German scientist feels, and not without cause, that had the government heeded the advice offered, the food problem would never have become acute in Germany. The advice given by an expert, on any subject, supposes always, that there is an adequate organization for putting the advice into operation. The fact that the organization, the German Government, was in a process of disintegration must never be lost sight of; and on the other hand, had a more intelligent food program been instituted doubtless the government could have lasted longer. At the very outset the government paved the way for trouble with the farmer by fixing prices for farm produce, and at the same time allowing labor and material to increase. If the law of supply and demand is to operate for one commodity it must operate for all. Nor did the matter of price fixing pass without serious objection in Germany.

In a rather broad way the German Government was advised to reduce stock to a livable minimum, thereby freeing a great deal of grain for human consumption, and at the same time have the population draw a larger percentage of nitrogen requirements from grain and vegetables. The scientist pointed out that 100 pounds of protein from grain passing through a hog or a steer would only deliver 20 to 23 pounds of protein in the form of meat. The scientist proposed to reduce the animals and free the vegetable protein for humans. If this were accomplished there would be less stock to feed with the result that it would not be necessary to grind out meals to a percentage where they would be inefficient as foods, and the discarded bran would be ample for the stock. The government, instead of following this rather broad program regarding grain, began by grinding out to 95 per cent, thereby at once reducing the available stock food, which resulted in a great slaughtering, an ample supply of meat for a short time but, in a long run, a meat shortage, undernourished work stock, and poor bread for the people. Instead of making the reduction artificially and gradually, thus allowing for proper care and storage of the meat against future needs, the nation glutted to-day and starved to-morrow. They point out that the stock was reduced, to which the scientist replies that it was not done scientifically.

The seemingly vacillating attitude of the government can be partly explained by the almost hysterical belief that the war was going to be short and decisive. By the time the government officials realized that a long war was ahead the food situation had been so permanently damaged by bad management that it was almost hopeless.

The fact that the hogs in Germany were reduced from 26 millions in 1914 to 8 millions at the present is of little value in proving the efficiency of the food control, when one realizes that this reduction was not done in any thought out attempt to increase food for humans, but was simply the result of a real food shortage. Had the reduction been made immediately, and the meat preserved, Germany would have found herself with more protein in the form of meat and vegetables and more calories. As it was, hogs were fed good human food far past the point of efficiency, and then slaughtered when there was nothing more for them to eat.

The scientists advised a rather flexible type of rationing, realizing full well the difficulties which a hard and fast régime presented from a dietetic standpoint. Opposed to this was the government policy which proposed an equal distribution with no regard for the justice of the same. To determine a just distribution based on

<sup>11</sup> Starling: The Significance of Fats in the Diet. Brit. Med. Jour., August 3, 1918.

sound dietetic principles was an almost impossible task, so the government took the easier if less efficient method. Rubner in 1917 advised a return to the normal method of allowing each person to determine his own ration. But the practical problems connected with Rubner's proposal were too complicated.

Many instances of clash of the scientific advisors and government administrators are obtainable. In each case the scientist prophesied unerringly the outcome unless his advice were taken and followed; on the other hand, the practical difficulties of meeting the advice offered were nearly insurmountable.

On February 15, 1919, the writer made the following report to the Supreme Economic Council in Paris in connection with the food situation and its development. This report, together with the charts, will show something of the events which led up to the final days of the war.

The German farmer bore the brunt of the war. His labor was taken for the army and the associated war industries, his animals were taken for military purposes, the prices he could receive for the staples were fixed at a not too high level, he was cut off from an adequate supply of fertilizer, he was given the task of feeding a greatly enlarged non-producing population; all this the farmer was expected to do and in addition he must, successfully to accomplish his task, overcome the annual German shortage of food, the 10 per cent which Germany in peace times had always found it necessary to import. At the very outset the food producers were under a heavy handicap. (See Chart I.)

Germany faced one of two alternatives, either to reduce the national food consumption or to increase the national production. Eventually she did the latter, though not until she had tried every possible way to get more food. There is no doubt but that the 10 per cent imported food was a luxus consumption, the average German was overweight and overfed and would have lived better and longer had he eaten less; but the German was a "good feeder," so it is not surprising to find that his first efforts looking to a solution of the food problem should be along the line of increased production, leaving the matter of decreased consumption to take care of itself, as it eventually has.

With this end in view the farmer was urged to increase his acreage, to make every effort to increase the yield, appeals being made to him along the lines of patriotism and duty. These did very well during the first enthusiastic days of the war. Eventually the government placed money premiums on increased plantings, 40 marks per hectare in the case of potatoes, and in addition offered large prizes to the Kreis showing the greatest relative increase. These efforts had their effects, naturally, and the acreage was increased, though, as a rule, the total yield was decreased, and every increase in acreage was made at the expense of some other necessary food product.

The course of events which took place rather followed the following lines: The British blockade, by cutting off importations to Germany, made an increased production imperative. To accomplish this end there resulted a general increased acreage, but owing to the fact that there was a labor shortage (men had gone to the army and war industries), an animal shortage (horses were taken for military use), and a fertilizer shortage (no guano could be imported and the lack of animals cut down the supply of manure), this increased acreage finally resulted in an actual decreased production, not only of food for humans, but of food for the stock as well. To overcome the shortage of grains and supply more bread the flour for baking was milled to 94 per cent; these high percentage flours cut off a great amount of bran which meant less stock food. The shortage of stock food led to undernourishment of the cattle, which was felt particularly in the milk and butter production as well as in the lowered meat supply. The latter was not so seriously felt, due to the fact that when there was a threatened fodder shortage the stock was killed to save it.

In this way the German hog supply was reduced from 26 millions in 1914 to less than 8 millions at present. Eventually this excessive slaughtering was felt in a greatly reduced meat supply, not only of pork, but of beef as well.

Thus there was set up in Germany a vicious circle of events, and any measures taken to relieve the pinch in one direction always caused an increased pressure in some other. It was a case of trying to overcome the 10 per cent handicap under which Germany was working, and due to the effectiveness of the British blockade this was impossible. Follow to its ultimate end any one of the problems which Germany faced in trying to solve her nutritional puzzle during the war and the trail will in the end lead to the blockade. All the juggling of food materials in Germany could not increase the total supply in the least, and as this supply annually became less and less, the pinch of hunger became more and more serious.

To show just how this correlation of activities worked out and to show statistically how pressure in one quarter caused serious results in another, three charts, V, VI, and VII, have been prepared. V shows graphically what was accomplished in a representative Kreis in the way of increased production. (Kreis Mayen is one of the most productive districts in Germany and figures from Mayen may be taken as a fair index to all agricultural Germany.) A study of this graph will show that, the importance of wheat and potatoes being realized, the total acreage planted to these foods was increased at the expense of barley and rye. In every case there is a decrease in the per hectare production due to the reasons already outlined. Only in the case of wheat is the total production increased, rye and barley with decreased acreage and decreased unit production show a decided total loss, while in the case of potatoes the increased acreage was not enough to overcome the loss per unit with a resulting decrease in total production.

The results of the decreased production of grains and potatoes are shown in Charts VI and VII. Chart VI details what happened to the cattle and the dairy products. The actual loss in the number of cattle was not as great as might have been expected, a loss of 20.5 per cent. This loss was greatest in the case of young stock, the milk cattle suffered a loss of 8.8 per cent, while the oxen, because of their great value as substitutes for horses, show a loss of only 2.8 per cent. From this it will be seen that the younger stock went, for the most part, to make up the meat supply of the country, this fact, together with the undernourished condition, accounting for the 30.5 per cent loss of dressed weight of carcasses. To-day the herds of Germany are for the most part composed of the older cattle. In the case of dairy products the undernourishment of the milch cows is strikingly shown by the large reduction in milk which amounts to 55 per cent. Considering that there has been only an 8 per cent reduction in the number of milch cows, this figure is enormous. Not only was the milk actually reduced in quantity, but it has suffered a decided lowering in quality, shown by the fact that in 1914 100 liters would produce 7.1 pounds of butter, while in 1918 100 liters would produce 6.2 pounds, a decrease of 12.7 per cent. A milch cow then, has lost 60 per cent of her 1914 efficiency. From this it can be seen that the crop shortages quite decidedly affected the stock situation, causing a reduction in the meat supply and a lowering in both the quantity and quality of the milk supply.

The final effects of the facts brought out in Charts V and VI are shown in Chart VII. At this point the population or the consumer is involved. There is a great reduction in the number of calories of food available; in 1913 the German consumed about 3000 C.<sup>12</sup> daily which in 1918 had dropped to between 1200 and 1400 daily, depending on the locality. The daily milk supply of the city of Coblenz fell from 22,000 liters in 1913 to 3000 liters in January, 1919. The fat supply in the same place was reduced from 300

<sup>12</sup>This figure has been arbitrarily set and is open to that criticism.

AVERAGE DAILY CONSUMPTION OF FOODSTUFFS  
GERMANY  
AVERAGE FOR 1912 & 1913

FOODSTUFFS.	CONSUMPTION			CONTRIBUTION FROM ABROAD			
	ACTUAL NUTRIMENT						
	PROTEIN	FAT	CARBO-HYDRATE	PROTEIN	FAT	CARBO-HYDRATE	CALORIES
	IN GRAMS			IN GRAMS			
	<b>I VEGETABLE FOODSTUFFS</b>						
VEGETABLE FOODS	46.2	5.0	411.0	1,916	6.6	0.4	40.4
GREEN VEGETABLES	3.1	0.5	15.5	80	0.1	0.0	0.6
FRUIT	0.9	1.4	16.9	87	0.2	0.4	5.4
SUGAR & HONEY	0.0	-	42.8	195	0.0	-	24.0
VEGETABLE FATS	-	7.6	-	71	-	6.5	-
COCOA	0.1	1.0	0.4	11	0.1	1.0	0.4
ALCOHOLIC LIQUORS	1.1	-	14.1	173 <sup>(1)</sup>	0.2	-	1.9
TOTAL	51.4	15.5	506.7	2,533	7.2	0.3	24.7
	<b>II ANIMAL FOODSTUFFS</b>						
MEAT & FATS	17.7	55.0	0.1	585	3.5	13.0	0.0
FISH	2.2	1.2	0.1	2	1.4	0.9	0.1
DAIRY PRODUCE	19.7	32.5	23.5	478	12.8	16.1	10.8
Eggs	1.9	1.8	0.1	26	0.8	0.7	0.0
TOTAL	41.5	90.5	23.6	1,109	18.5	36.7	18.9
	<b>III TOTAL FOODSTUFFS</b>						
	92.9	106.0	530.5	3,642	25.7	45.0	43.6
							715

(1) Including 112 calories of alcohol

(2) Including 11 calories of alcohol

PER CAPITA TOTAL AND WEEKLY AVERAGES OF ALL FOODS  
ISSUED IN BONN, GERMANY, BY SIX MONTH PERIODS  
FROM JULY 1, 1916 TO JANUARY 1, 1919

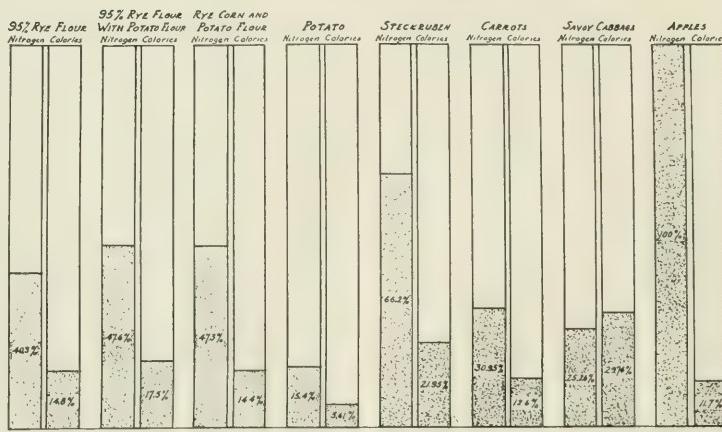
All Figures Are In Grams	1 July 1916 to 1 January 1917	1 January 1917 to 1 July 1917	1 July 1917 to 1 January 1918	1 January 1918 to 1 July 1918	1 July 1918 to 1 January 1919
	11 Eggs				
Meat	3338	5,168	4,490	3,910	2,525
Sausage	4,508	2,070	1,340	720	685
Bacon	425	1,400	200	100	-
Total	8,271	8,658	6,630	4,730	3,210
Average per week	318.06	332.37	231.93	181.92	123.47
Fish	4,320	135	-	-	203
Eggs	11	11	8	7	8
Cheese	62.5	50	50	125	337
Butter	860	630	680	760	950
Lard	305	30	150	100	80
Margarine	335	735	505	710	300
Oil	-	105	120	70	-
Total	1700	1,500	1,435	1,640	1,330
Average per week	65.64	57.69	55.95	63.10	51.16
Bread	50,890	46,500	47,500	47,750	49,625
Average per week	1,957	1,788.96	1,826.92	1,836.54	1,908.65
Cereals	8,625	8,050	5,300	6,150	5,550
Average per week	370.20	309.60	211.53	236.54	213.46
Rice, Sago	-	125 (Kcal)	250 (Kcal)	-	-
Legumes	750	730	100	-	350
Sugar	4,500	4,150	4,900-7,400	5,300	7,650
Average per week	173.08	160	1885-28442	203.85	294.23
Marmelade	750	2,375	3,500-6,000	5,875	2,625
Potatoes	95,500	52,500	63,250	111,500	98,500
Average per week	3,673.08	2,019.23	3278.05	4,288.46	3,788.46
Potato Flour	-	-	425	425	250
Turnips	4,000	4,800	15,000	51,000	-
Vegetables	-	5,375	2,300	9,625	750

ANALYSIS BY HALF YEAR PERIODS  
Daily Allowances

Protein	42.59	39.62	36.67	39.85	34.41
Fat	20.42	19.44	12.85	19.06	10.49
Carbohydrate	298.25	287.61	290.25	326.22	298.67
Calories	1587.43	1440.43	1460.00	1619.81	1463.19

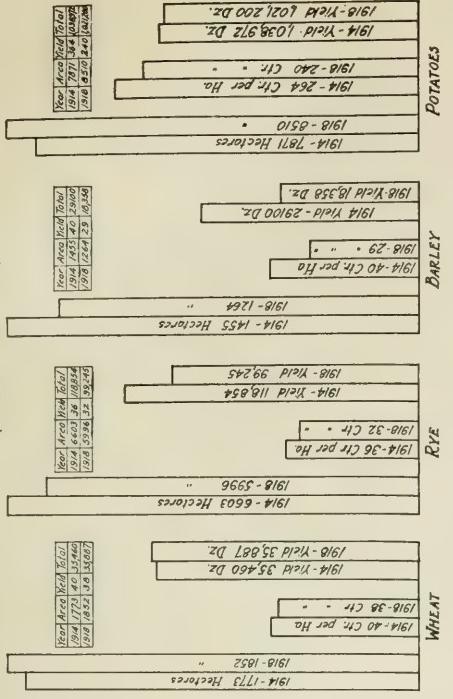
## DIGESTIBILITY OF FOODS

TOTAL COLUMN REPRESENTS 100 UNITS  
PORTION SHADeD RED REPRESENTS AMOUNT LOST IN DIGESTION  
PORTION UNSHADeD RED REPRESENTS AMOUNT UTILIZED BY BODY



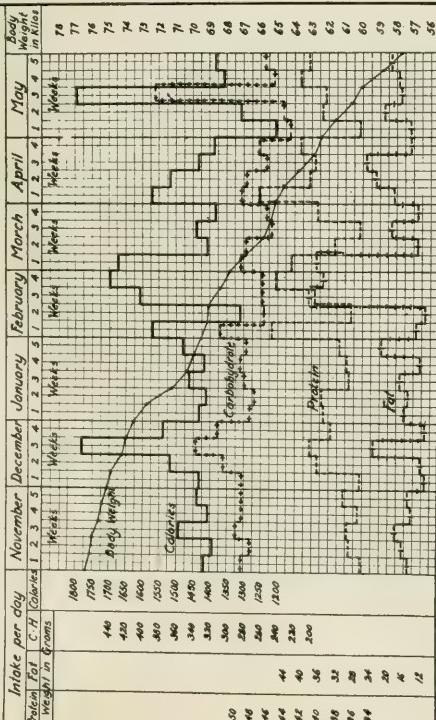
V

*CHANGES IN ACREAGE, PRODUCTION AND YIELD OF STAPLES  
GERMANY, 1914 TO 1918  
(STATISTICS FROM MAIEN)*



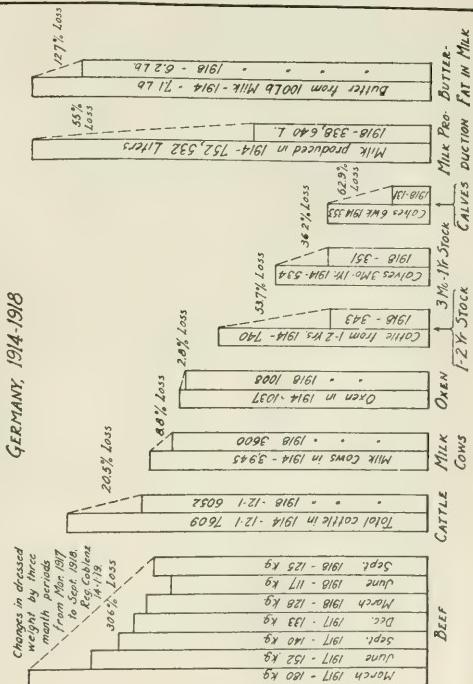
VI

*INFLUENCE OF THE RATIONED FOOD ON BODY WEIGHT  
Nov. 1916 to Mar. 1917, Bonn, Germany*



VII

*DECREASES IN MEAT, MILK AND CATTLE  
STATISTICS FROM COELLEN,  
GERMANY, 1914-1918*



grams per capita per week in 1913 to 30 grams per capita per week in 1919. Meat, which had been furnished at the rate of 140 grams per person per day in peace times, was reduced to the low figure of 20 grams in 1919. Bread and potatoes both suffered a 50 per cent reduction, and in the case of bread the quality fell as much.

By following through the rather involved and ramified activities of the Germans in their attempts to overcome the 10 per cent handicap in food supplies and to feed the vast number of non-producers connected with the war machine, it becomes increasingly clear that the greatest barrier between the German people and an adequate food supply was the British fleet.

The failure to increase production is the main part of the story, though by no means all of it, the problems of control and distribution being also of great importance. Dr. Neumann, of the University of Bonn, after a careful study of the whole question states that in his opinion if there had been complete control of food supplies in Germany the population would have been one-third better fed. During the early days of the war the great patriotism of the people together with the popularity of the war made control rather easy. As the war wore on and food became scarcer and scarcer the farmer gave up his excess less and less willingly, especially when he found that he could sell illegally at very high prices. There were many ways to evade the law, and no doubt all were used. Long after it had been officially announced that certain foods were off the market or the supply exhausted one could still obtain them provided adequate payment was made. This fact made it possible for the well-to-do to have ample supplies most of the time. Further studies into this matter of control made it quite evident that the government did not control the food as far as would appear on first examination. Towards the end of the war, when there was nothing but defeat staring Germany in the face, the Reichs government became very weak, and the farmer who had borne the burden of the fight grew less and less tractable, giving smaller and smaller amounts of food.

For the first time in history the world at large faces a universal food shortage. Heretofore scarcity of food has been only local, the famines of India and Ireland being well-known examples, and in these cases it was always possible for other countries to get food to the lands of shortage. To-day there seems reason to believe that in the whole world there is not all the food which could be consumed by all the people. The war, with its numberless ramifications, especially its connection with the food question, has driven into the public mind the fact that after all there is something to be learned about mass feeding, or public rationing. There seems little doubt that a new type of work is going to be developed, food control. It is well to make clear that there are real differences between food control and rationing. Food control can be a success, mass rationing will always be a failure. By food control, as the term is now used, is meant a control of those activities which tend to dissipate the energy contained in food and a more complete conservation of the same. Broadly speaking, any activity which tends to raise the price of any article of food above its normal level tends to destroy the usefulness of the food and in that way works against the greatest public good. Under this type of activity we can class such things as useless transportation, too many middlemen, or withholding foods from the market in order to maintain a price. Inasmuch as such procedures tend to keep the food out of the hands of the consumer they work against fullest conservation of national resources. Along the lines of positive control there is a great deal of work to be done on the stock question, the relationship

which must exist between the number of people and the amount of livestock to be maintained. This problem alone played a quite important part in the German food question all during the war. Then the control of live stock is intimately wrapped up with the question of the milling of flours, the choice of grains to be milled, the percentage to which they shall be made of the millings.

All these are new problems, problems which must be studied and worked over for years to come. It will need the combined work of the nutritional expert, the economist, the railroad man, the politician, the psychologist, and the housewife to ever reach any satisfactory working basis; more than that, it will have to meet with the approval of the people. But such steps must in no wise tend to hinder the people from choosing and buying what they wish when they wish it. The average person is by far the best judge of his own nutritional needs; the proof lies in the fact that the race continues to live and live a normal, healthy life. Any person or group of persons which attempts to set down a hard and fast ration for the masses will soon find a sick, discontented nation of people.

From a study of the feeding problem it would appear that the real question of calculating scientifically, according to the best findings of physiology and nutrition, the exact needs of the average man is rather simple, and can be done with the accuracy of any mathematical problem. But no mere scientist can possibly take into account in such calculations the personal likes and dislikes of each individual, the racial dietetic habits, the sectional dietetic habits, the climatic dietetic demands, the thousand and one daily variations in the psychical make-up of each individual, and to make a ration satisfactory all these things must be considered. To ration a race we must assume the infinite amount of work which each person is capable of doing much more efficiently and satisfactorily for himself. Germany tried it and failed, England contented herself with control and succeeded.

We can draw some very important conclusions from the experiences of England and Germany in relation to this problem of mass feeding under conditions of famine, blockade, or siege.

1. Food control, *i. e.*, food conservation must be practiced by every person.
2. Live stock must be reduced to a level compatible with the grain supply.
3. The people must subsist on a larger percentage of vegetable products, increasing the amount of land used for such crops as rapidly as such land is freed from the support of live stock.
4. Bread will form the staple of diet, so the milling of the flour must be carried out in the most efficient manner, taking into consideration the actual nutriment to be given to humans and to stock.
5. Rationing must be limited to those articles which are luxuries; necessities, *i. e.*, bread, meat, potatoes, etc., must be permitted to circulate freely. (In case of actual siege or practically closed blockade it may become necessary to enforce stringent rationing.)
6. The psychological aspects must never be overlooked.

## LITERATURE

Appended is a list of the more important literature issued during the war on the subject of food control and food rationing. The reader is especially referred to the British Food Journal, the Reports of the British Food Committee, and the German official statement of the situation as found in "Die deutsche Volksernährung und die englische Aushungerungsplan" by a committee headed by Eltzbacher.

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## PATHOLOGICAL CHANGES IN THE GASTEROPOD LIVER PRODUCED BY FLUKE INFECTION

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Because of the significant contributions that have been made to normal metabolism by a study of pathological conditions, the writer has been prompted to make a study of the liver of certain gasteropod species commonly infected with larval flukes, with the view of discovering the normal metabolic processes of the host, the changes occasioned by the parasitism, and the application of these data to comparative pathology.

The data on histological pathology of animals induced by helminth parasitization are indeed meager. Text-books on pathology make little or no mention of the gross lesions and symptomatology and give nothing at all on the more detailed pathological pictures of such lesions, because so little first-hand investigation of the subject has been made. This is especially true of diseases of the hepatic organ caused by helminth parasites, the significance of which is little understood. Since the properties of secretion, absorption and excretion are common to the hepatic gland of the snail and the vertebrate, a study of the infected liver of the snail justifies itself as one of comparative pathology which is readily interpreted in terms of vertebrate pathology.

The material on which this study is based consists of many thousand sections of water pulmonates from all over the United States, from South America (*Planorbis guadelupensis*), and from South Africa (*Physopsis africana*). In addition, living *Planorbis trivolvis* and *Physa sp.* have been used in microchemical tests and analyses. Many of the specimens from which sections have been prepared have been fixed in corrosive-acetic or corrosive-nitric mixtures, but some have been killed in corrosive sublimate alone and others, as a check, in formol-alcohol. Sections have been uniformly cut 8  $\mu$  thick and stained in Delafield's hematoxylin with eosin counterstain. To some of these sections Best's potassium-ammonium-carmine stain has been added to check the iodin tests for glycogen.

### THE NORMAL GASTEROPOD LIVER

The gross structure of the gasteropod liver was worked out by Swammerdam (1737), who described and correctly figured the main features of the organ. Later workers have not materially altered this classical description. No attempts at a detailed histological study of the mollusk liver were made

until the middle of the nineteenth century, when Leydig (1850) published his monograph on *Paludina vivipara*. Since that time numerous students of histology and physiology have published their researches, which, on the whole, are decidedly conflicting and contradictory.

The liver of the gasteropod consists of racemose tubules which arise from two embryological outpocketings from the mid-intestine. The tubules are lined with glandular epithelium and are bound together by a meshwork of interstitial cells in which are found branches of the hepatic artery, blood lacunae, bile-ducts and numerous nerve endings. The whole gland is enclosed in an epithelial sac, the tunica propria. Although the cells of the tubules and their respective functions have been the subject of intensive analysis, little attention has been paid to the intimate structure of the intertubular portions of the organ and their relations to the tubules.

Some investigators have found as many as four kinds of epithelial cells opening into the lumen of the tubule, but most workers have described three. Barfurth (1883) has designated these as ferment cells, liver cells and lime cells. The ferment cells of Barfurth are referred to by Biedermann and Moritz (1899) as secretion cells and the liver cells as resorption cells. Frenzel (1884) has attacked Barfurth's theory that the lime cells contain tri-calcium phosphate granules. Although Barfurth's proof is certainly open to question, Frenzel's critique is unconvincing.

The data justify the belief that the epithelial cells of the tubule act as a digestive organ in the secretion of diastatic and peptic ferment, that they are the mediary absorptive organ for glycogen, fats and peptones, and that they function in the excretion of certain types of wastes.

Contrary to the view of the European workers, who have recognized at least three types of cells in the epithelium of the tubule, the writer is obliged to conclude that there are, from a purely cytological standpoint, only two kinds, the rhomboidal or tetragonal cells with large spherical nuclei (the lime cells of Barfurth), and the more common kind, irregularly palisade in character, with small oval nuclei, comprising both the ferment and the liver cells of Barfurth.

The "Lime Cell."—Barfurth (1883: 500) states that the water snails differ from the land species in that the "lime cells" are entirely lacking in the former and are always present in the latter. Despite this statement the writer has consistently found the type of cell in which Barfurth claims that tri-calcium phosphate crystals are stored up, in all normal liver tissues of *Planorbis trivolvus*, *P. guadelupensis*, *Physa gyrina*, *Physa* sp., *Lymnaea proxima*, *Goniobasis carinifera*, and *Physopsis africana* (see Fig. 1). The make-up of this cell is not essentially different from the "lime cell" of *Helix pomatia* figured by Schneider (1902: 570, Fig. 477). In normal uninfected tissues it is roughly rhomboidal in shape and is situated basally, seldom opening into the lumen of the tubule. The nucleus is usually spheroidal with many distinct chromidial granules and a large karyosome. At times the outline of the nucleus becomes irregular, suggesting a polymorphonuclear condition. The cytoplasm is decidedly

reticular, with large opalescent spheroidal or ovoidal granules entirely filling the interstices between the threads of the reticulum. These are the granules which Barfurth has claimed for land pulmonates to be the tri-calcium phosphate deposits. Evidence in support of Barfurth's thesis is decidedly lacking. Provided the investigator was able to get a test for both phosphorus and calcium and to isolate tri-calcium phosphate from the tissues, even then the circumstantial evidence constitutes no proof that these elements exist as this salt in the so-called "lime cells." Moreover, the fact that these cells have been found in every normal tissue of water pulmonates examined by the writer, together with Barfurth's statement that tri-calcium phosphate does not occur in water pulmonates, constitutes strong evidence against Barfurth's theory. Furthermore, these deposits in the "lime cells" are not crystalline, as demonstrated by the petrographic microscope, and, while tri-calcium phosphate may exist as a colloid, the behavior of these granules in pathological cells favors the view that they are not lime cells. It is quite possible, as Frenzel suggested (1884: 326), that they may be phosphoproteins, but their reactions to dyes suggests a relationship to basic proteins. It is certain that these cells serve a very specialized function in storing up food masses.

*Ferment and Liver Cells.*—These cells have been described as distinct types by certain authors. The ferment cells are believed to be unique in the secretion of enzymes which aid in digestion, whereas the liver cells are those in which storage of reserve food takes place. In addition, excretory functions have been assigned to each of these types. Cytologically the writer is able to recognize only one type; physiologically he is able to find many kinds of types which grade into each other almost imperceptibly. The single type of cell, which appears to contain within itself the properties of digestion, absorption and secretion, is palisade in structure, with an oval nucleus in the basal third and an elongate distal end which extends to the opening of the tubule (Fig. 1). In the region of the liver tubule the ends of these cells are protected by a pseudo-cuticula which stains as a mucoid. The changes which have been described and which have given rise to the differentiation of ferment and liver cells are those induced by: (1) The preparation and secretion of digestive enzymes; (2) the taking in by absorption of carbohydrate (stored as glycogen), fats and proteins; and (3) by the elimination of wastes of an excretory nature. In view of the fact that this type of cell is comparable in part to the vertebrate liver cell, the term *liver cell* should be preserved and used for both liver and ferment cells of authors.

During a period of feeding the liver cells are rich in glycogen and fat inclusions and may also test for proteins foreign to the protoplasm. During hibernation and enforced starvation these food products for the most part disappear and frequently large vacuoles appear in the cytoplasm. Likewise, during hibernation and at other times when the respiration is low, excretory granules accumulate in the vacuoles. Under conditions of optimal metabolism these granules are found singly or at most in small aggregates.

#### MACROSCOPIC APPEARANCE OF INFECTED SNAILS

In order to examine a snail for parasites the apex of the spire is carefully removed, exposing the tip of the liver. The entire animal is then removed through the artificial opening. Normal liver tissue has a characteristic brownish-yellow appearance, differing considerably in the exact shade at various times according to the kind of food consumed. In *Planorbis* the tunica propria is fairly well separated from the liver tissues proper. In some other species it is thin and closely applied to the tubules, so that their outline is readily made out from gross inspection. But infected material, especially if the infection is heavy, may usually be detected by the removal of the shell. The liver portion is puffed out and, if the infection is severe and of long duration, frequently tubercular in appearance. In *Planorbis* the red of the blood has been lost and, in its place, in the case of infection with several kinds of flukes, a reddish-brown or yellowish-brown pigment is found in the tissues of the parasite. The pigment suggests a process similar to the production of bile pigment from the hemoglobin of the vertebrate red blood corpuscles. In many species of invading parasites (monostomes, amphistomes, eye-spotted distomes) the melanin pigment of the parasite shows through the tunica propria of the host. In other cases the definite outlines of the parasite sporae-sacs are seen through the epithelium. Usually under these conditions the host tissue looks a sickly yellow. A very delicate prick with the needle produces a lesion in the tissues through which in heavy infections the parasites pour forth in large numbers.

#### METHOD AND ROUTE OF INFECTION

The animal at the time of immigrating into the mollusk (the miracidium stage) and at the time of emigrating (the cercaria stage) has spines for mechanically piercing the host tissues and a secretion is poured forth that digests away the cells of the snail that lie in the path of the parasite. These organs are substantially aided by the muscular equipment of the fluke, and especially in the case of the cercaria by the acetabular suctorial apparatus.

Authors state that the miracidium wanders into the host and changes into a sporocyst. Leuckart (1901: 263-265) has seen the miracidia of *Fasciola hepatica* swarm around *Lymnaea trunculata* soon after the two species had been placed in the same aquarium. While some clung to the muscle of the foot and others to the mantle fold, still others worked their way up the breathing pore into the lung. The writer's findings are thoroughly in accord with Leuckart's further suggestion that the invaders follow the course of the blood and finally lodge in the liver tissues. Evidence that the invasion is through the blood and lymph channels and not through the lumina of the liver tubules is twofold: (1) The parasites are always found in the connective tissues and the interstices between tubules, while the portions of the epithelial cells bordering on the lumina are always intact except in the most necrotic tissues. (2) The food which the parthenita takes in first of all is from the lymph. This accounts for the pigment so frequently seen in the body of the sporocyst and the gut of the redia. This

method of invasion is different from that of the liver fluke as it enters the definitive host, in which case the actual transfer to the digestive tract of the sheep is passive and the passage is by way of the bile-duct. But it does conform to the general method and route of the blood flukes, which do not encyst but bore their way through the skin into the lymph sinuses and finally secure a circulation in the blood.

#### PATHOLOGY OF INFECTED LIVER CELLS

As soon as the miracidium secures a lodgment in the tissues of the mollusk an irritation is set up, as is evidenced by the nervous movement of the mollusk. Certain larvae which bore into the resistant muscles of the foot soon become tightly lodged there and never reach a breeding place. Those which get into the blood stream are at most only slightly injurious to the host until they reach the liver sinuses. Lodgment here places the flukes in the direct course of food distribution and, with the metamorphosis into the sporocyst, growth begins. Germ balls arising parthenogenetically increase the bulk (Fig. 2). When a second parthenitic generation is producing cercariae the bulk of the parasites has been increased enormously over the original microscopic size. Indeed, a heavily infected snail may contain a far greater amount of parasites than its own net size or weight. Aside from the energy required to carry it about, the pressure on the tubules is such that the lumina are almost completely closed and consequently the food supply is lessened. When this means of relieving pressure is used to its utmost the tunica is tightly stretched. Under such circumstances the least prick of a needle causes a rupture, through which lymph and parasites are squirted out. Such a direct mechanical burden is distinctly dangerous to the infected host, but this burden is augmented by the food ration demanded from the host in increasing amounts as the parasite develops.

Rapid increase in number and size of the individuals of the brood developing in the parthenita depends primarily on the available food. This must be furnished by the host. The location of the parasite in the blood sinuses of the liver or, as in the case of some fluke parasites, in the gills, intercepts the food supply of the host in transit to the organs. Microchemical evidence supports the view that most of these food-stuffs are requisitioned by the very young germ balls, in which a large amount of glycogen, fats and undigested proteins are found. In case of the close apposition of the fluke to the epithelium of the host (Fig. 3), these materials pass through from host to parasite without ever reaching the blood.

This heavy drain on the food supply of the host is easily demonstrated. Under normal feeding conditions snails which are not infected give a heavy test for glycogen, fats and proteins throughout all of the cells of the epithelium of the tubules. Most of the glycogen and fats are in the liver cells, while the protein storage cells give a heavy test for protein materials. On the other hand, heavily infected tissues give at most only a very scanty test for foodstuffs in the epithelium, a fairly heavy test in the intertubular sinuses, and a decidedly heavy test in the parasites. That the parasite makes direct use

of these foods is thus proved, but whether the several enzymes which are required for absorption and assimilation are localized in certain cells or are the general property of all the cells remains to be actually demonstrated.

When the supply of available foods has been exhausted the parasite has usually reached a state of development where motile cercariae are present. These, by their continued jerking back and forth free themselves from the parthenita. In practically all species glands are present which help to digest the cells of the host. In this they are usually aided by powerful acetabula by which attachment to a particular group of cells is effected and the digestive processes thus accelerated. First the connective tissue cells of the sinuses are broken down and the cytoplasm utilized. It appears, however, that the nuclei are more difficult to digest. Then the epithelial cells of the tubules are subjected to the cytolytic action. By this time, however, other more truly pathological conditions have developed, due to the excretory wastes of the parasites which have accumulated in the host tissues.

**Excretions.**—The normal excretory process in the liver cells is effected directly by the formation of vacuoles within the cytoplasm of the epithelial cells and their extrusion into the lumina of the tubules. At times small concretions of protein katabolism are found within these vacuoles. The content of the vacuoles, whether fluid or solid, is eosinophilic, and the cytoplasm immediately around these vacuoles frequently tests acid. Thus it is seen that the route of excretion in the immediate vicinity of the liver cells is just the reverse of that of digested food.

The effect of the parasite on the excretory process of the mollusk is twofold. The host is required to dispose of the parasite's excretory wastes and by the various pathological processes initiated within the host tissues increasing amounts of its own nitrogen and other decomposition products must be disposed of. Part of the wastes from the parasite goes into solution in the lymph and is passed on to the kidneys, but a large group of developing flukes in a blood sinus soon come to form an obstruction which produces a stasis sufficient to cause an accumulation of waste products at that particular focus. The amount of this wastage from the parasite is very great. In hibernating conditions (encysted) the fluke may accumulate an amount of excretory wastes several times the size of its own body.

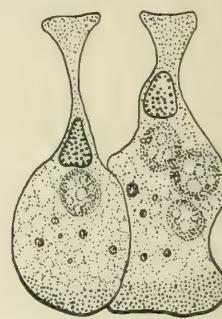
The greatest harm results, however, from the cytolytic and cytotoxic effect of these parasite wastes on the host. While certain harmful effects obtain from the mechanical burden of the fluke and from its consumption of food intended for the tissues of the snail, the pathological picture is much more intensified by the direct effect of the secretions and excretions of the parasite. The normal reaction of the epithelial tissues of the liver is alkaline, although the presence of excretory materials may cause an acid reaction in the immediate vicinity of such wastes. But the parasite, when once thoroughly established in the blood sinuses, tends to produce an acid reaction throughout the entire tissue. It is important to note, however, that the snail is able to a marked degree to counteract this

acidity by rapidly filtering the wastes through the epithelium into the lumen. This tends to preserve an alkaline condition at the base of the cells nearest the point of attack of the parasite, while the free ends of the cells are usually quite acid.

The first reaction of either type of epithelial cell to the abnormal products caused by the parasite is to work these out of the cytoplasm into vacuoles which are forced toward the free end of the cell and extruded into the lumen (Figs. 2, 5, 6, 7). But the ability to make this adjustment is limited, and failing to eliminate the poisons forced into the system, the



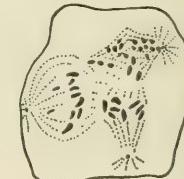
TEXT FIG. 1.



TEXT FIG. 3.



TEXT FIG. 2.



TEXT FIG. 4.

TEXT FIG. 1.—"Lime" cell of *Pl. trivolvis* with large excretory vacuoles and concretions resulting from infection with *C. convoluta*. ( $\times 1080$ .)

TEXT FIG. 2.—Polymorphonuclear "lime" cell of *Pl. trivolvis* extruding chromidia through cell wall into lumen of tubule; infection as in Text Fig. 1. ( $\times 1462$ .)

TEXT FIG. 3.—Liver cells of *Pl. trivolvis*, showing large number of excretory vacuoles and granules due to infection with *C. acanthostoma*. ( $\times 1462$ .)

TEXT FIG. 4.—"Lime" cells of liver of *Planorbis trivolvis*, showing multipolar spindle due to tissue infection with *Cercaria convoluta*. ( $\times 1080$ .)

host cells are subject to characteristic lytic changes. Previous to this time the glycogen and fats which had been absorbed by the liver cells have passed through into the blood sinuses and thence into the developing flukes. But the parasites seem to be unable to utilize the protein particles stored up in the "lime" cells and these begin to degenerate. They accumulate in dense agglomerates between the nucleus and the free end of the cell (Fig. 5, Text Fig. 1), taking on a dense basophilic stain. Their reaction is suggestive of a complex mucoid. Little by little these dense agglomerates become worn away and finally dispersed throughout the cell. Closely associated with this type of katabolism is the breaking down and extru-

sion of chromidia from the nucleus and cytoplasm (Fig. 6, Text Fig. 2). These trophic granules have probably played an important part in the anabolism of the cells. They are normally distributed throughout the liver cells, but are especially numerous in the region of the food particles. They may be precipitately extruded from the cell (Text Fig. 2), or, like the protein food agglomerates, may degenerate into eosinophilic particles and add to the excretory wastes (Text Fig. 3).

A further pathological change in the nuclei of the protein cells is the formation of multipolar spindles (Text Fig. 4). Karyokinesis is not common in adult snail liver tissues but may be found. In pathological tissues such as these, normal mitoses are all but wanting, while abnormal divisions are common. Figures with three or four trophic centers are the most common. Amitotic division has not been seen.

All of these processes, which have mainly involved the more striking types of katabolism within the infected tissues, are accompanied by a degeneration of the cell walls, especially at the free end of the cells (Fig. 7), where the greatest concentration of toxic products occurs. However, it is an astonishing fact that snails, in which cytolytic changes have become very pronounced, are still able to feed and to carry on the digestive processes, although necessarily imperfectly.

It seems probable that the fluke cannot continue its existence indefinitely by parthenogenetic propagation, even when the circumstances are unfavorable for its migration or transference to another host. Under these circumstances the parthenita degenerates and the cercaria either encysts or works its way out of the snail. If encystment is to occur, the tail of the cercaria is thrown off and a cyst capsule is formed around the worm. This ameliorates the conditions of the host and a readjustment is effected. A hypertrophy of interstitial cells results around the cysts. Thus fibromata are formed in which melanin granules are frequently laid down (Fig. 4). This is the only way by which the snail is known to occlude foreign bodies. No calcification has been found in these fibromata. Meanwhile, the epithelial tissues are recuperated by rapid multipolar divisions of liver and "lime" cells basally and a sloughing off of the necrotic tissues into the lumen.

Among the secondary effects of the disease of the liver tissues brought about by these pathogenic organisms is the inability of the host to prevent such undigested food and feces as normally pass down the main digestive tract from entering the lumina of the liver. The poisoning of the tissues also involves the main digestive tube so that the cilia of the intestinal epithelium fail to function. Under these condition diatoms and algal filaments, together with particles of silica, frequently get into the ultimate tubules of the liver.

Although it has not been possible to determine any marked difference in the resistance of the various species of snails studied, there is evidence for the belief that certain flukes are much more harmful than others in their effects on the host. From a study of the cercariae, the conclusion is reached that organs for mechanical injury, such as hooks and spines, are less likely to prove baneful to the host than the by-products

of the worm. And while the excretory wastes set up a decidedly abnormal condition, the secretions of the mucin glands are probably the most injurious of all to the host. Such digestive secretions are commonly found to be present in echinostome cercariae, stylet cercariae and furcocercariae. Certain species of furcocercariae (*Cercaria gigas*, cercaria of *Schistosoma mansoni*) even have two physiologically different kinds of such digestive glands, those which are eosinophilic and those which are basophilic (Fig. 7). The protoplasm of the eosinophilic glands is deep red while the nuclei are basophilic. The basophilic mucin glands, on the other hand, take a deep hematoxylin stain throughout. The reaction of this latter type to Best's calcium-ammonium-carmine stain suggests that the granules around the nuclei of the cells are closely related to glycogen, while the material in the ducts gives a pure mucin reaction.

#### DISCUSSION

Since the liver of the mollusk possesses the properties of secretion, absorption and excretion in common with the vertebrate liver, and since the structure of the organ is in part similar in mollusk and vertebrate, it is profitable to inquire whether the study of the pathological conditions in the liver of the snail has a direct bearing on infected liver tissue of the vertebrate. This is especially worth while since some twelve adult species of flukes are known to give rise to pathological conditions in the liver of man.

First of all it is noteworthy that the fluke infection in the mollusk liver is by way of the blood system, while that of the great majority of parasitic infections of the vertebrate liver is by way of the bile-duct. Coccidiosis, hydatiditis, and most of the fluke infections arise from a previous lodgment of the parasite in the digestive tract, a migratory inflammation of the epithelium of the bile-duct as the infective agent forces its way up the duct, and finally the spreading of the disease throughout the trabeculae of the liver. Then with the breaking down of the epithelial cells the matrix cells are invaded. Primary inflammation induced by such an invasion of animal parasites gives rise to a catarrhal condition of the epithelium, to an enlargement of the bile-duct and to a diffuse eosinophilia.

There are, however, a few common types of fluke parasitization of the vertebrate in which liver infection is not developed by way of the bile-duct but rather from the blood stream. In such infections the connective tissue surrounding the blood vessels is first attacked and the epithelium of the trabeculae remains relatively untouched. This condition is followed by stasis of the portal vein and the development of granulomata around the infected area. As far as is known all of the blood flukes (including species of *Schistosoma* and *Bilharziella*) effect an entrance directly or indirectly into the blood stream and finally come to reside in the blood sinuses in the liver. Possibly also certain monostomes which live in the blood stream are at least temporary parasites of the liver tissues. Animals in this location can secure assimilable food much more readily than those in the lumen of the digestive tract or in its outpocketings.

Disregarding the means of entrance of the parasite and the primary pathological picture, there is a striking similarity in mollusk and vertebrate livers parasitized by flukes. Macroscopically both are distended and changed in color from the normal. Hypertrophy of the interstitial cells and desquamation of the epithelial cells occur in both, although in the opposite order. Hyperplasia, which is common in the vertebrate host, has not been seen in the mollusk liver. Edema and ascites may be found in both. The fluke in the blood sinus of the mollusk liver produces a recognizable stasis, just as *Fasciola hepatica* gives rise to bile stasis in the sheep and *Schistosoma japonicum* to portal stasis in man. Mechanical and chemico-pathological lesions are common in both instances. Melanin deposition in the connective tissue is a matter of record in mollusk and vertebrate liver. Necrosis is the ordinary fate of pathological tissues in every case where the infection is prolonged. And finally, with the migration of the pathogenic agent, rapid recovery of the organ by proliferation of new cells is the rule in mollusk and vertebrate liver alike.

On the whole, the mollusk liver seems able to withstand a heavier infection for a longer time than the vertebrate liver. It is also able to effect recovery much more readily. This suggests a greater power of adaptability and a larger regenerative index, based, no doubt, on a simpler organization.

#### SUMMARY

1. The tubular epithelium of the mollusk liver consists of two cytologically different kinds of cells, those with large nuclei and with closely aggregated opalescent granules in the cytoplasm (the "lime" cells), and those with small nuclei in which glycogen and fat are frequently found (the liver cells).

2. These two types of cells carry on secretive, absorptive and excretive processes in a manner similar in part to such processes in the vertebrate liver.

3. The liver tissues of many mollusks (mostly gasteropods) are infected with flukes which pass the parthenogenetic generations and the larval phase of the hermaphroditic generation in the mollusk. Heavy infections can usually be recognized by macroscopic inspection of the body after removal from the shell.

4. The flukes work their way to the liver through the blood sinuses, coming to reside in the interstices between the liver tubules. Here they mechanically irritate the host, requisition a large amount of digested foodstuffs, empty a burdensome amount of excretory wastes into the tissues, and cause serious cytolytic changes both in the epithelial cells of the tubules and in the intertubular connective tissue.

5. The pathological picture of the infected gasteropod liver is on the whole decidedly suggestive of the condition set up in the vertebrate liver infected with pathogenic organisms.

**EXPLANATORY NOTE.**—It was necessary in the absence of the author to reduce materially the length of this article and to make certain changes in the text. Figures 6 and 7 were drawn by Dr. Faust in color, but were replaced by copies in black and white. Responsibility for the changes in the manuscript and for the accuracy of the substituted drawings is therefore assumed by

me. It is with great pleasure that I acknowledge the counsel and cooperation of Mr. Brödel.

Ralph G. Mills, M.D.

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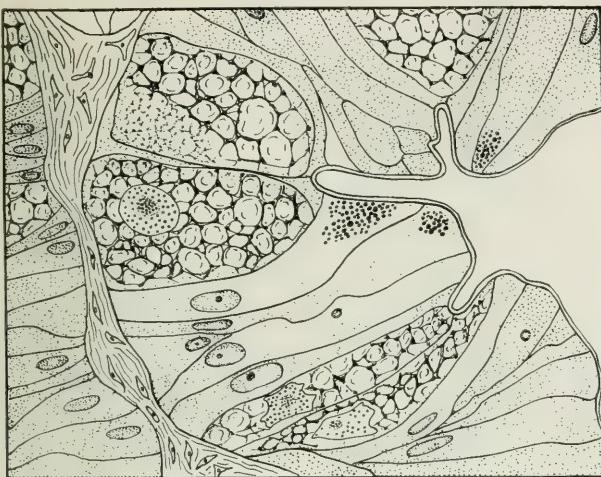


FIG. 1.—Normal liver tissue of *Planorbis triolvis*, showing "lime" cells and liver cells of tubule, pseudo-cuticula lining the lumen of the tubule and the inter-tubular connective tissue. Note glycogen granules just beneath pseudo-cuticula. ( $\times 810.$ )

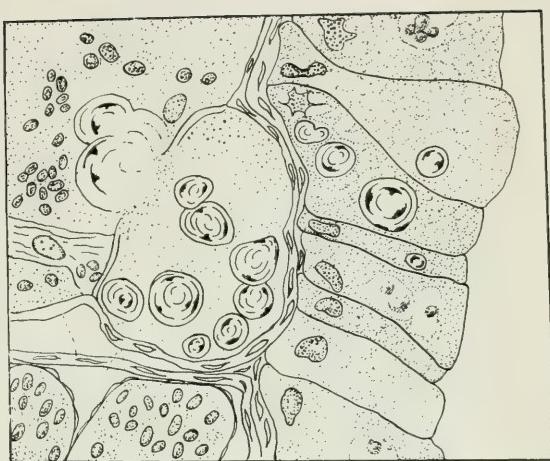


FIG. 3.—Effect of *Cercaria isocotylea* on *Pl. triolvis*. Note passage of large masses of food from the epithelial cells into the parasite. ( $\times 810.$ )

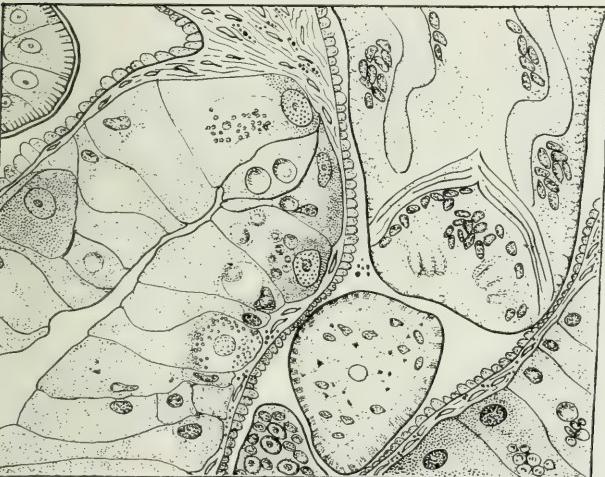


FIG. 2. Pathological liver tissue of *Pl. triolvis* infected with sporocysts and developing cercariae of *Cercaria gigas*. Note position of flukes in connective tissue. Epithelium of tubules highly vacuolated; glycogen only in connective tissue and in sporocysts. ( $\times 810.$ )



FIG. 4. Late stage of infection of liver of *Pl. triolvis* with *Cercaria convoluta*. Note hypertrophy of connective tissue, with fibromata. ( $\times 810.$ )



FIG. 5.—Effect of *Cercaria micropharynx* infection on liver epithelium of *Lymnaea proxima*. Note degeneration of nuclei and food reserves of protein-storage cells, excretory granule formation and eosinophilia at free end of epithelial cells ( $\times 1080$ .)



FIG. 6.—Liver tissue of *Goniobasis carinifera* infected with *Cercaria quatuor-solenata*. Note large aggregations of excretory granules, extrusion of chromidia, and general eosinophilia of epithelial cells. ( $\times 1080$ .)

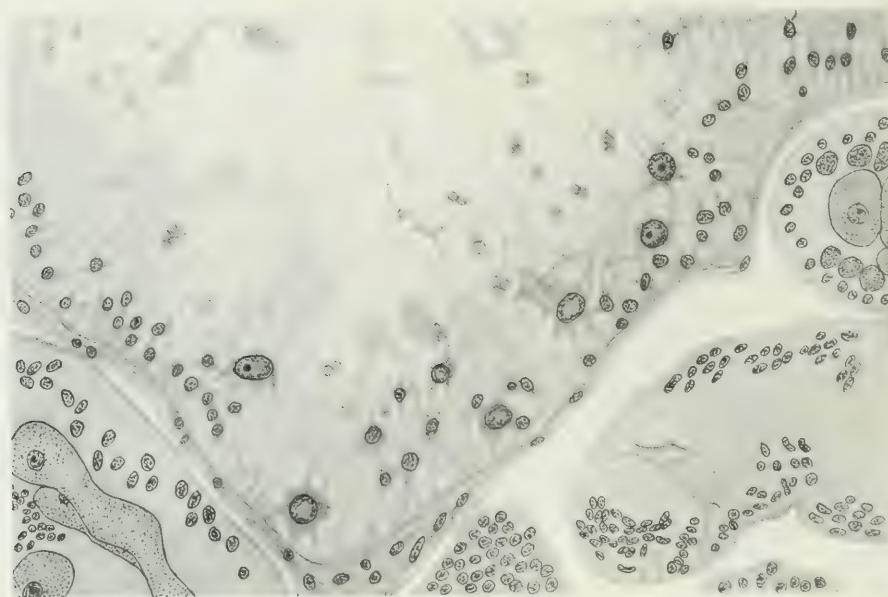


FIG. 7.—Effect of Cercaria of *Schistosoma mansoni* on liver tissue of *Planorbis guadelupensis*. Note heavy production of excretory granules, eosinophilia and general necrosis of cells. ( $\times 1080$ .)

### III. THE FATE OF INFLUENZA BACILLI INTRODUCED INTO THE UPPER AIR PASSAGES

By ARTHUR L. BLOOMFIELD

(From the Biological Division of the Medical Clinic, The Johns Hopkins University and Hospital)

In previous papers<sup>1</sup> we reported observations on the fate of certain bacteria after their introduction into various parts of the upper air passages. This work represented a portion of a systematic study of one phase of infection, namely, the period from the arrival of the organism at the mouth or nose until it is eliminated or until disease is produced. *Sarcina lutea*, *B. coli*, and *Staph. albus* were studied. It was found that these bacteria were rapidly disposed of; *Sarcina* was promptly destroyed by the saliva, and *B. coli* and *Staph. albus* were washed away by mechanical processes without showing any tendency to colonize. The present report deals with a similar study of the hemoglobinophilic bacteria (*B. influenzae*). No attempt was made to produce disease, and our purpose was simply to study the fate of the organisms and the method of their disposal.

#### LITERATURE

Several records of inoculations of human beings with *B. influenzae* are found in the recent literature. These experiments were all made on the hypothesis that the organisms used might be the cause of epidemic influenza and in the attempt to demonstrate this fact by the production of disease. Rosenau<sup>2</sup> introduced strains of influenza bacilli freshly isolated from cases of epidemic influenza into the throats of volunteers without producing any local or general disease. Sellards and Sturm,<sup>3</sup> in the course of a study of hemophilic bacilli isolated from cases of measles, sprayed a saline emulsion of five strains upon the mucous membranes of the eye, nose and throat of four volunteers. Cultures made at three-day intervals for a period of two weeks were uniformly negative, and no local or general symptoms were produced. Sellards reports no observations made during the first three days after inoculation. Wahl, White and Lyall<sup>4</sup> found that the application to the mucous membrane of the nares and naso-pharynx of a saline emulsion of strains from cases of epidemic influenza failed to produce any abnormal symptoms in five healthy men. These workers were unable to recover *B. influenzae* from the nose after 48 hours except in one case, but found the organisms present in the naso-pharynx for two weeks or longer. In some cases the bacteria disappeared after a few days to return later. In summary, then, the above experiments, while indicating the general trend of events, give no detailed information about the immediate and exact fate of the influenza bacillus.

#### METHODS

*Strains.*—Until the needs of the recent epidemic stimulated the development of media satisfactory for the growth of *B. influenzae*, little success had been met with in the study of the finer details of its natural history or in the differentiation of strains by biological or other methods. All small

Gram-negative hemophilic bacilli isolated from the respiratory passages were placed together in one group. Recent work, however, particularly that of Rivers,<sup>5</sup> suggests that all the organisms previously included under one head are by no means identical, but that they represent various groups differing in essential biological characteristics. It is therefore impossible to be certain now of the exact nature of the original organism of Pfeiffer as well as of the nature and identity of the "influenza bacilli" which were so prominent in the cases of epidemic disease in 1918.

Three strains were employed in the present work. They were all isolated from the throats of healthy men,\* and conformed to all the usual criteria of the influenza bacillus group.

*Media.*—In view of the difficulty of growing influenza bacilli under unfavorable conditions, the utmost care was used in the preparation of the media. Fresh 2 per cent meat infusion agar (pH 7.3 to 7.5) to which 1 per cent of fresh defibrinated rabbit's blood was added, or the sodium oleate hemoglobin agar of Avery were used in all the work. The medium was always fresh and moist, and each lot was tested by inoculation with the various strains. It was considered unsatisfactory unless the colonies were large and reached their maximum growth in from 24 to 36 hours.

*Inoculations.*—As in the previous work, healthy individuals presenting no unusual abnormality of the upper air passages were used. The whole 24-hour growth from an agar slant was collected on a loop and deposited on the desired site—the tongue, nasal septum, naso-pharynx or tonsil crypt. Cultures were made at various intervals by scraping the site of inoculation with a platinum loop or (in the case of the naso-pharynx) by means of the usual cotton swab. The material collected was spread with a glass rod over two plates. It was regarded as essential that the spread of colonies be discreet; plates covered by a confluent mass of growth are useless in work of this sort. The cultures were studied after from 24 to 48 hours, and in every case the diagnosis of *B. influenzae* was established by isolation of the organism in pure culture. Great care was taken in estimating the quantitative relations.

The site of inoculation was watched for signs of reaction. In no case was there any change in the appearance of the mucosa, or any constitutional reaction.

#### EXPERIMENTS

**Exp. I.**—Fate of influenza bacilli swabbed on the tongue. The bacteria were placed on the tongue, and cultures were made from the tongue and from the pharynx at various intervals. The results are summarized in Table I.

*Summary.*—Influenza bacilli swabbed on the tongue in large amounts were promptly spread over the mouth cavity. The

\* We are indebted to Dr. Rivers for these strains.

TABLE I.—FATE OF *B. INFLUENZÆ* SWABBED ON THE TONGUE

Name	Date	Procedure	Number of colonies of <i>B. influenzae</i> per plate recovered from tongue and pharynx												Control culture before inoculation	
			Tongue						Pharynx							
			After 10 min.	After 2 hrs.	After 1 day	After 2 days	After 3 days	After 4 days	After 10 min.	After 2 hrs.	After 1 day	After 2 days	After 3 days	After 4 days	Tongue	Pharynx
M.	Nov. 10.	One slant strain 55 <i>B.</i> swabbed on anterior half of tongue.	∞*	A good many colonies <i>B.</i> infl.	A very few colonies <i>B.</i> infl.	No <i>B.</i> infl.	....	....	A good many colonies <i>B.</i> infl.	No <i>B.</i> infl.	No <i>B.</i> infl.	No <i>B.</i> infl.	....	....	No <i>B.</i> infl.	A few cols. <i>B.</i> infl.
J.	Nov. 16.	One slant strain 55 <i>B.</i> swabbed on anterior half of tongue.	∞	A very few cols. <i>B.</i> infl.	No <i>B.</i> infl. found.	....	....	No <i>B.</i> infl.	∞	150 cols. <i>B.</i> infl.	20 cols. <i>B.</i> infl.	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.	A few cols. <i>B.</i> infl.
C.	Nov. 17.	One slant strain 63 swabbed on anterior half of tongue.	∞	150 cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	A few cols. <i>B.</i> infl.	A few cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.	
B.	Nov. 17.	One slant strain 33 swabbed on anterior half of tongue.	∞	A few cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	Many cols. <i>B.</i> infl.	A few cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.	

\* ∞ = innumerable.

TABLE II.—THE FATE OF INFLUENZA BACILLI INTRODUCED INTO THE NOSE

Name	Date	Procedure	Number of colonies of <i>B. influenzae</i> per plate recovered from nose and pharynx												Control culture before inoculation			
			Nose				Pharynx											
			After 10 min.	After 2 hrs.	After 1 day	After 2 days	After 10 min.	After 2 hrs.	After 1 day	After 2 days	After 4 days	After 8 days	Nose	Pharynx				
C.	Nov. 11.	One slant strain 55 <i>B.</i> swabbed on left nasal septum.	∞	∞	1000 cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	A few cols. <i>B.</i> infl.	No <i>B.</i> infl.	No <i>B.</i> infl.	....	....	No <i>B.</i> infl.	A few cols. <i>B.</i> infl.				
S.	Nov. 12.	One slant strain 55 <i>B.</i> swabbed on left nasal septum.	∞	200 cols. <i>B.</i> infl.	No <i>B.</i> infl.	No <i>B.</i> infl.	....	No <i>B.</i> infl.	A few cols. <i>B.</i> infl.	About 50 cols. <i>B.</i> infl.*	....	No <i>B.</i> infl.	No <i>B.</i> infl.	No <i>B.</i> infl.				
St.	Nov. 13.	One slant strain 55 <i>B.</i> swabbed on left nasal septum.	∞	200 cols. <i>B.</i> infl.	20 cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	No <i>B.</i> infl.	No <i>B.</i> infl.	No <i>B.</i> infl.	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.				
Ch.	Nov. 18.	One slant strain 63 swabbed on right nasal septum.	∞	50 cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	About 20 cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	No <i>B.</i> infl.	A few cols. <i>B.</i> infl.				
B.	Nov. 19.	One slant strain 33 swabbed on left nasal septum.	∞	Several hundred cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.				

\* This strain was not 55 *B.* (See Table V.)

TABLE III.—FATE OF INFLUENZA BACILLI INTRODUCED INTO TONSIL CRYPTS

Name	Date	Procedure	Number of colonies per plate of <i>B. influenzae</i> recovered from crypt and pharynx												Control culture before inoculation		
			Crypt						Pharynx								
			After 10 min.	After 2 hrs.	After 1 day	After 2 days	After 4 days	After 6 days	After 8 days	After 10 min.	After 2 hrs.	After 1 day	After 2 days	After 4 days	After 6 days	After 8 days	Crypt
Co.	Nov. 25.	One loop strain 33 placed in a tonsil crypt.	300 cols. <i>B.</i> infl.	10 cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	....	Many cols. <i>B.</i> infl.	Many cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.
H.	Nov. 29.	One loop strain 63 placed in a tonsil crypt.	∞	∞	....	100* cols. <i>B.</i> infl.	200* cols. <i>B.</i> infl.	No <i>B.</i> infl.	No <i>B.</i> infl.	Several hundred cols. <i>B.</i> infl.	Several hundred cols. <i>B.</i> infl.	....	Several hundred cols. <i>B.</i> infl.	Several hundred cols. <i>B.</i> infl.	About* 100 cols. <i>B.</i> infl.	No <i>B.</i> infl.	A few cols. <i>B.</i> infl.
W.	Dec. 6.	One loop strain 55 <i>B.</i> placed in a tonsil crypt.	About 100 cols. <i>B.</i> infl.	A few cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	....	Many cols. <i>B.</i> infl.	A few cols. <i>B.</i> infl.	No <i>B.</i> infl.	....	....	....	No <i>B.</i> infl.	No <i>B.</i> infl.

\* Not strain 63. (See Table V.)

organisms disappeared both from the tongue and pharynx very rapidly. After two hours the number recovered was much reduced, and after 24 hours only a very few organisms were obtained in two out of four cases. Control cultures before inoculation yielded a very few colonies from the pharynx in two cases. The general result of this experiment is that in 24 to 48 hours the inoculated organisms have disappeared or at least been reduced to the number "normally" present in the pharynx. There was no local or general reaction following inoculation.

**EXP. II.**—Fate of influenza bacilli introduced into the nose. The bacteria were deposited on the nasal septum behind the vestibule and cultures were made at various intervals from the nose and pharynx. The results are summarized in Table II.

**Summary.**—Large numbers of *B. influenzae* swabbed on the nasal septum disappeared rapidly from the site of inoculation. None could be recovered after 48 hours. Simultaneous cultures from the pharynx in three of five cases yielded a few colonies of *B. influenzae* in from two hours to 24 hours after inoculation. In one case (S.) 50 colonies were recovered from the pharynx in the 48-hour culture, but this organism was found to be a different strain from that introduced (see Table V).

**EXP. III.**—Fate of influenza bacilli introduced into tonsil crypts. The bacteria were introduced into a tonsil crypt with a platinum loop and cultures were made at various intervals from the crypt and from the pharynx. The results are summarized in Table III.

**Summary.**—Influenza bacilli introduced into tonsil crypts could not be recovered from the site of inoculation after 24 hours in two of three cases. In the third case influenza bacilli were recovered after two and also after four days, but they were found to be different strains from those introduced (see Table V). In this case influenza bacilli were also recovered from the pharynx several days after inoculation, but the strain was not only different from that introduced, but it was also different from that obtained from the crypt after two and after four days (see Table V).

**EXP. IV.**—Fate of influenza bacilli introduced into the naso-pharynx. Influenza bacilli were swabbed on the naso-pharynx and cultures were made at various intervals. The results are summarized in Table IV.

**Summary.**—Influenza bacilli swabbed in large amounts on the naso-pharynx disappeared very rapidly. After two hours very few organisms could be recovered from the site of inoculation. In one case, influenza bacilli recovered after one and after four days were different strains from those introduced (see Table V).

#### DISCUSSION

The general result of these experiments seems to indicate two facts: First, that several strains belonging to the group of so-called influenza bacilli swabbed in large amounts on the normal mucous membranes of the upper air passages failed to colonize and disappeared in about a day; and secondly, that in no case did they produce any demonstrable local lesion or general reaction.

In five instances influenza bacilli were recovered at periods later than 24 hours after inoculation. It seemed of importance to determine whether these strains were identical with those introduced or whether the strain introduced had disappeared and another had supplanted it. Biological differential methods worked out by Dr. Rivers were applied by him to the study of these cultures. In every case it was possible to show that the strain introduced had been replaced by organisms possessing different characteristics (see Table V). It seems desirable to bring these findings into relation with the known facts

about the presence of influenza bacilli in the throats of healthy people. Winchell and Stillman<sup>6</sup> review the recent literature on this subject and report careful studies of their own on a series of individuals over a period of eight months. It seems quite certain that hemophilic bacilli may be found in from 40 to 80 per cent of various groups of healthy people. The exact seat of bacterial multiplication in the pharynx and the length of time over which any given strain persists are however unknown. Our experiments suggest that the free surfaces of the normal mucous membranes present a relatively unfavorable environment for these bacilli to colonize upon. It may be that their source in certain cases is a focus, such as a chronic sinusitis, bronchitis, or bronchiectasis, or an acute infection of the respiratory tract either in the same or in another individual from which they are discharged into the open pharyngeal cavity. It should be emphasized that all studies on the persistence of influenza bacilli in the throat are of uncertain significance in the absence of proof that the strains recovered from the same individual at various times are identical. The final solution of this question must await the development of complete and accurate methods of differentiating the various strains of hemophilic bacilli.

Inasmuch as the organisms employed in our experiments had been grown on artificial media for several generations the objection may be raised that their failure to colonize was due to alteration in their virulence by growth outside the body. This objection cannot be answered and the experiments are presented with this in mind.

#### THE MECHANISM OF DISPOSAL OF *B. INFLUENZÆ*

As in the case of the organisms previously studied an attempt was made to analyze the various factors which might be responsible for the disposal of *B. influenzae*.

**1. The Antagonistic Action of Other Bacteria in the Mouth and Throat.**—No direct experimental method was available for determining to what extent the growth and multiplication of *B. influenzae* in the throat is prevented by bacteria already present. It is known that *B. influenzae* grows well on artificial media in symbiosis with many other bacteria under proper quantitative relations. It may, however, be rapidly overgrown by an excess of other bacteria which in smaller numbers would favor its growth. In the case of nasal inoculations other bacteria can hardly play an important part since the nasal mucosa is practically free of organisms.

**2. The Effect of the Mouth Secretions.**—An attempt was made to reproduce mouth conditions by testing the effect of saliva on influenza bacilli in the test tube. Fresh saliva was centrifuged at high speed for a few minutes to remove gross particles. Small amounts of the resulting clear fluid were placed in test tubes and heavily inoculated with *B. influenzae*. The entire growth from an agar slant was suspended in 0.5 c. c. of saliva, and control tubes of plain broth were similarly inoculated. Cultures were made at various intervals on oleate hemoglobin agar plates. Three salivas covering the normal

TABLE IV.—FATE OF INFLUENZA BACILLI INTRODUCED INTO THE NASO-PHARYNX

Name	Date	Procedure	Number of colonies per plate recovered from naso-pharynx					Control culture before inoculation
			After 10 min.	After 2 hrs.	After 1 day	After 2 days	After 3 days	
W.	Dec. 1.	One slant of strain 33 swabbed on naso-pharynx.	∞	200 cols. B. infl.	No B. infl.	No B. infl.	.....	No B. infl.
R.	Dec. 1.	One slant of strain 33 swabbed on naso-pharynx.	∞	10 cols. B. infl.	A very few* cols. B. infl.	.....	4 cols. B. infl.*	No B. infl.

\* Not the strain which was introduced. (See Table V.)

TABLE V.—COMPARISON OF CHARACTERISTICS OF STRAINS OF INFLUENZA BACILLI INTRODUCED AND RECOVERED IN VARIOUS CASES

Name	Characteristics of	Morphology	Staining	Hemoglobinophilia	Hemolysis	Indol formation	Nitrite formation	Agglutination with stock serum
Sp.	Strain introduced (55 B). Strain recovered from throat 48 hrs. after inoculation.	Small regular bacilli. Small regular bacilli.	Gram-neg. Gram-neg.	Hemoglobinophilic Hemoglobinophilic	Non-hemolytic. Non-hemolytic.	Marked. None.	Marked. Marked.	+
Ha.	Strain introduced (63). Strain recovered from throat 4 days after inoculation. Strain recovered from crypt 4 days after inoculation.	Small regular bacilli. Small regular bacilli. Large thick bacilli.	Gram-neg. Gram-neg. Gram-neg.	Hemoglobinophilic Hemoglobinophilic Hemoglobinophilic	Non-hemolytic. Non-hemolytic. Hemolytic.	None. Marked. Marked.	Marked. Marked. Marked.	0 0 0
R.	Strain introduced (33). Strain recovered from throat 24 hrs. after inoculation. Strain recovered from throat 3 days after inoculation.	Small regular bacilli. Very large numerous threads.	Gram-neg. Gram-neg. Gram-neg.	Hemoglobinophilic Hemoglobinophilic Hemoglobinophilic	Non-hemolytic. Non-hemolytic. Non-hemolytic.	Marked. None. None.	Marked. Marked. Marked.	0 0 0

TABLE VI.—EFFECT OF SALIVA ON INFLUENZA BACILLI

Date	pH. of saliva	Strain of B. infl.	Time of culture after inoculation	0.5 c. e. broth and growth from one slant B. infl.	0.5 c. e. saliva and growth from one slant B. infl.
Dec. 6.	7.0	55 B.	Immediately.	Innumerable cols. B. influenzae.	About 50 cols. "mouth bacteria" per plate + innumerable cols. B. influenzae. About 50 cols. "mouth bacteria" per plate + innumerable cols. B. influenzae. About 300 cols. "mouth bacteria" No B. influenzae.
			After 2 hrs.	Innumerable cols. B. influenzae.	
			After 24 hrs.	Innumerable cols. B. influenzae. (About same number as in previous culture.)	
Dec. 6.	7.0	33	Immediately.	.....	About 100 cols. "mouth bacteria" per plate + innumerable cols. B. influenzae. About 75 cols. "mouth bacteria" per plate + innumerable cols. B. influenzae. About 500 cols. "mouth bacteria" per plate. No B. influenzae.
			After 2 hrs.	.....	
			After 24 hrs.	.....	
Dec. 3.	7.3	63	Immediately.	.....	About 300 cols. "mouth bacteria" per plate + innumerable B. influenzae. About 300 cols. "mouth bacteria" per plate + innumerable B. influenzae. About 300 cols. "mouth bacteria" per plate. No B. influenzae.
			After 2 hrs.	.....	
			After 24 hrs.	.....	
Dec. 3.	7.3	33	Immediately.	.....	About 50 cols. "mouth bacteria" per plate + innumerable B. influenzae. About 75 cols. "mouth bacteria" per plate + innumerable B. influenzae. About 500 cols. "mouth bacteria" per plate. No B. influenzae.
			After 2 hrs.	.....	
			After 24 hrs.	.....	
Dec. 4.	6.4	55 B.	Immediately.	.....	About 100 cols. "mouth bacteria" per plate + innumerable B. influenzae. About 75 cols. "mouth bacteria" per plate + innumerable B. influenzae. About 100 cols. "mouth bacteria" per plate. No B. influenzae.
			After 2 hrs.	.....	
			After 24 hrs.	.....	

range of reaction (pH 6.4 to pH 7.3), and three strains of influenza bacilli were employed. The results are summarized in Table VI.

This experiment shows the following points. Influenza bacilli suspended in plain meat infusion broth were viable at the end of 24 hours. From saliva inoculated with the same amount of culture living influenza bacilli were recovered after two hours, but not after 24 hours. The proportion of mouth bacteria in the saliva to the inoculated influenza bacilli was about 1 to 10,000 at the beginning of the experiment. At the end of 24 hours there was only a slight increase in the number of mouth bacteria, whereas no influenza bacilli grew. The experiment seems therefore to indicate that while saliva exercises no immediate destructive effect on *B. influenzae*, it is an unfavorable medium for the growth of these bacteria and that they do not remain viable in this medium for as long as 24 hours. This result was constant with salivas of different pH.

The probable explanation, therefore, of the rapid disappearance of *B. influenzae* when introduced into the normal upper air passages involves both the action of a medium unfavorable for the growth of these organisms, together with the mechanical flushing processes constantly at work in these regions.

The question naturally arises in this connection as to what makes possible the tremendous growth of influenza bacilli in disease conditions, such as acute sinusitis pharyngitis, laryngitis, pneumonia, measles, influenza, etc. A possible explanation which still lacks final proof is that these acute processes may alter the environment in such a way that the organisms take hold and grow rapidly at the seat of disease.

#### SUMMARY

- Three strains of influenza bacilli introduced in large amounts into the normal upper air passages disappeared very rapidly—within from one to two days. In no case was a carrier state produced.

- In no case did any local or general pathological process result from such inoculation.

- In five instances influenza bacilli isolated later than 24 hours after inoculation were shown to be different strains from those introduced.

- Influenza bacilli were no longer viable after being suspended in saliva for 24 hours at 37°C.

- The rapid disappearance of influenza bacilli from the upper air passages is probably due to the combination of an unfavorable environment with the mechanical flushing processes at work in these regions.

- The question of the persistence of influenza bacilli in normal throats cannot be finally settled until we possess accurate methods for differentiating various strains of hemophilic bacteria.

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## NOTES ON MUSCULAR WORK DURING HYPNOSIS

By NORMAN CLIVE NICHOLSON \*

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The novel conditions of modern warfare have directed attention to the extraordinary occurrence of the functional nervous and mental disturbances. With one-third of all discharges for disability in the British Army due to war neuroses or so-called "shell shock," these disorders became a grave medico-

military problem calling for urgent therapeutic solution. Treatment with rest, re-education, psycho-analysis, occupational therapy and hypnosis was and still is being tried, but from reports in the British and French medical journals it would appear that the most encouraging results are obtained with the aid of suggestion and hypnosis.

Unfortunately, however, our knowledge of hypnotism is very incomplete, and if it is to be used intelligently as an effective means of analyzing and treating these conditions, it is necessary that it be given a sound physiological foundation. Thus far there have been scarcely any carefully conducted laboratory experiments to determine the underlying physiology of hypnosis. What data we have are in large part unsupported by experimental proof—a deficiency which obviously lessens its scientific worth. Valuable contributions have been made to the subject, it is true, by such men as Vogt, Forel, Bernheim, Moll and others, but these are concerned mainly with the therapeutic application and general psychology of hyp-

\* It is a deep sorrow that along with the appearance of this article we must record the untimely death of the author. The son of the Reverend J. C. Nicholson, pastor of Madison Square Methodist Episcopal Church, but 28 years old, Nicholson had shown himself a man of unusual energy and promise. He was one of those who early in his student years had manifested an interest in study and research the first-fruits of which were published in an article with Dr. Emil Goetsch, in the American Review of Tuberculosis, in 1919. Obliged early in January, 1918, to interrupt his studies because of ill health, his energy and enthusiasm were undiminished. In the fall of 1919 he returned, himself again physically and full of activity and devotion to his chosen career. In his death his friends and his teachers mourn the loss of an active, inquiring mind, which gave promise of happy fruition.

notism. Nowhere, in fact, has there been any consistent program aiming to get at the subject by the method of laboratory experimentation. It therefore occurred to the writer that the time was ripe to bring to bear on the problem the modern technique of the physiological laboratory and thus to obtain a series of exact objective records of just what effect hypnosis and suggestion have on the body mechanism of man. The completed investigation will aim naturally to answer the following questions: What is the condition of the muscular, the nervous, the cardio-respiratory, the gastro-intestinal, the endocrine and the excretory systems in the hypnotic sleep and how can these systems be influenced by suggestion? Notes on the different phases of the work will be published as they are completed. This preliminary report concerns only the results of certain studies on the muscular system.

As we wished to determine the effects of suggestion upon muscular efficiency and record the findings objectively, a Mosso ergograph was used as the instrument best adapted to fulfil these requirements. With this apparatus one arm and one hand are so fixed by straps and metal supports that it is possible to test the efficiency of a small group of muscles. The person experimented upon makes a series of short contractions of the flexor muscles of the middle finger, thereby lifting a known weight to a definite height which is recorded upon a drum. In a set of experiments the rate of the series of contractions, that is, the interval of rest between the contractions, is kept constant as also is the load lifted. Under these conditions a fully awake subject makes contractions which become less and less extensive as fatigue comes on, until finally, despite the strongest voluntary effort, the contractions of the muscles are insufficient to lift the weight. In this way a record is obtained, such as is shown in Fig. 1, and the capacity for work of the muscle used can be studied objectively under varying conditions and permanent records secured. The contractions in the experiments here reported were timed by a metronome so that they occurred at regular intervals of two seconds. Any irregularity in the rate of revolution of the drum, that is, any difference in the spacing between the separate lines in the records may therefore be disregarded. The weight used was one of three kilograms.

The objection might be advanced that with the Mosso ergograph we cannot compute the total amount of work which the muscle is capable of performing, as would be possible if we were to use a spring ergograph. But a consideration of the nature of our problem will show that relative results are adequate for our purposes and that the ergograph of Mosso is therefore best suited for these experiments.

Only those subjects were used whom I could place in the deepest hypnotic sleep—the state characterized by cataleptic rigidity.<sup>1</sup> Having selected the subjects, it was necessary to determine the normal work capacity of each one as measured by the ergograph. Accordingly, for a period of two weeks daily tracings were obtained until an approximately standard curve of work for each subject in the waking condition was

established. Fig. 1 represents such a standard work-curve requiring approximately 10 minutes to complete. The next step was to determine the normal recuperative period, that is, the length of time necessary to enable the subject to repeat the amount of work just recorded and thus reproduce a tracing as extensive as the first. This period varied with the different subjects, but was never more than two nor less than one hour.

With these standards determined for the waking state we proceeded to compare them with the results obtained in the hypnotic sleep. A similar procedure was followed for each subject as follows:

EXP. I.—Subject hypnotized and given suggestions, throughout the period of work, of increased energy and muscular power with absence of fatigue sensations, and the results recorded (Fig. 2). The subject was awakened when the tracing had extended around the circumference of the drum, which generally took about 20 minutes.

EXP. II.—In this experiment an answer was sought to the question: How much work is the fully awake subject capable of performing immediately after the work done in hypnosis? That is, a tracing was made of his work capacity as soon after the completion of Experiment I as a fresh drum could be put in place—about three minutes (Fig. 3).

EXP. III.—Subject again hypnotized at the conclusion of Experiment II and a second tracing in the hypnotic sleep recorded at once (Fig. 4).

EXP. IV.—Subject while fully awake was permitted to work almost up to the point of fatigue and while still working he was hypnotized and thus in one tracing the contrast between work in the waking and hypnotic sleep was recorded (Fig. 5, A and B).

EXP. V.—Subject was permitted to work almost up to the point of fatigue, but at the point where in the previous experiment hypnosis had been induced suggestions were now made without hypnosis of increased muscular power, no fatigue sensations, etc. (Fig. 6, A and B).

#### RESULTS

The records obtained show that a very definite increase in muscular efficiency can be obtained by suggestion in the hypnotic state and that suggestions given even while the subject is fully awake influence muscular efficiency to some extent. The increased efficiency during hypnosis shows itself in three ways: First, by an increase in the actual amount of work done (Figs. 2, 4, 7). In fact, during the hypnotic sleep the capacity for work seemed practically endless, as we invariably had to conclude the experiment because of the limited recording surface of our drum. Further work along this line is of course essential. The records secured so far afford, however, an affirmative answer to the question: Can suggestions during hypnosis increase work capacity? Second, by an increase in endurance (Figs. 2, 4, 7). Third, by a decrease in fatigue, both subjective and objective. After work in the hypnotic sleep the subjects never complained of any fatigue, nor could questioning elicit any signs of fatigue, whereas after performing a much smaller amount of work in the waking condition they frequently complained of being quite tired and exhausted and always on being questioned stated they were fatigued. The records (Figs. 2, 4, 7) show the absence of any objective fatigue, but this point was brought

<sup>1</sup>In all of the experiments the hypnotizing was done by the author.

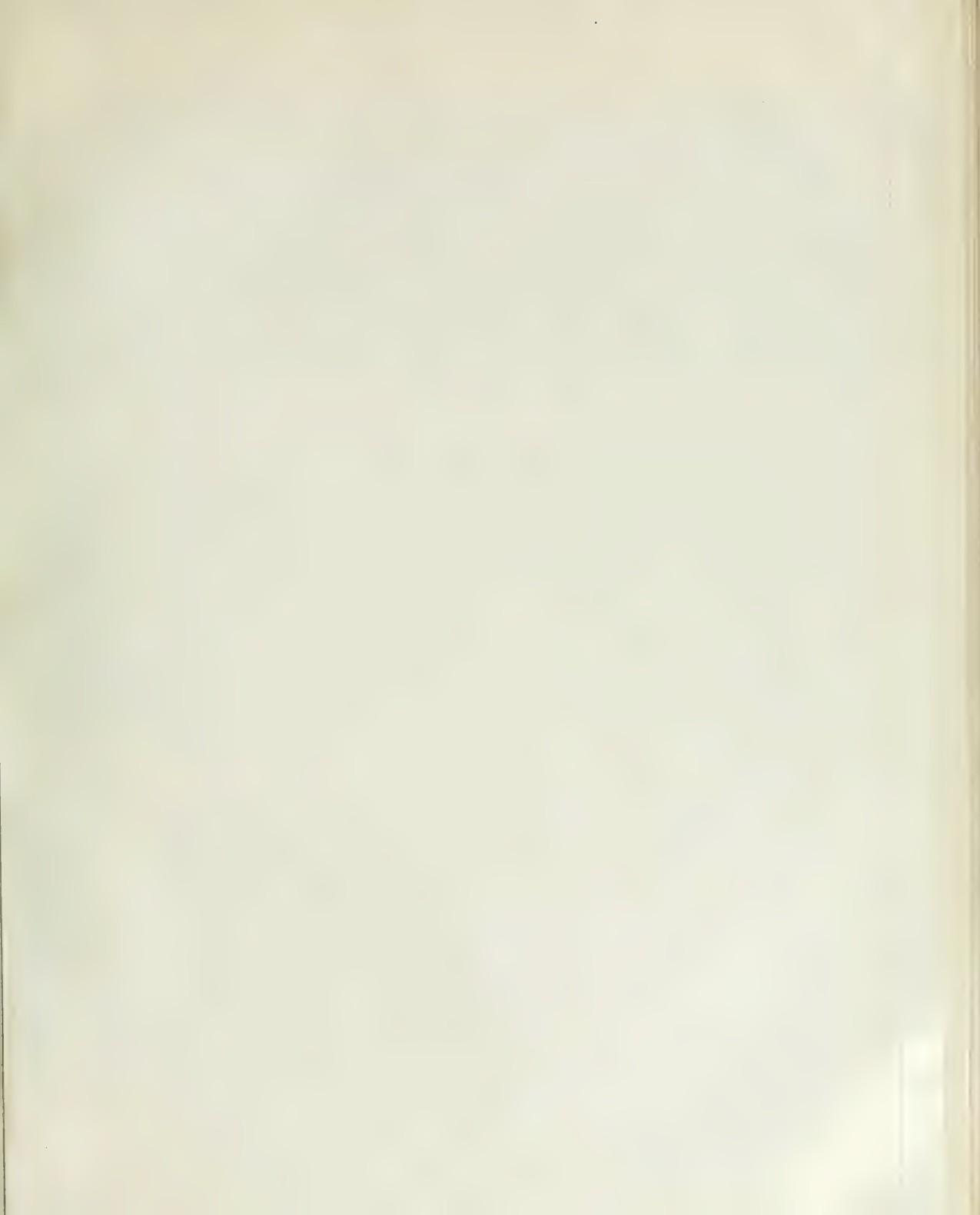




FIG. 1.—Standard fatigue curve of subject when fully awake. It requires a rest period of one hour to enable the subject to duplicate this amount of work.

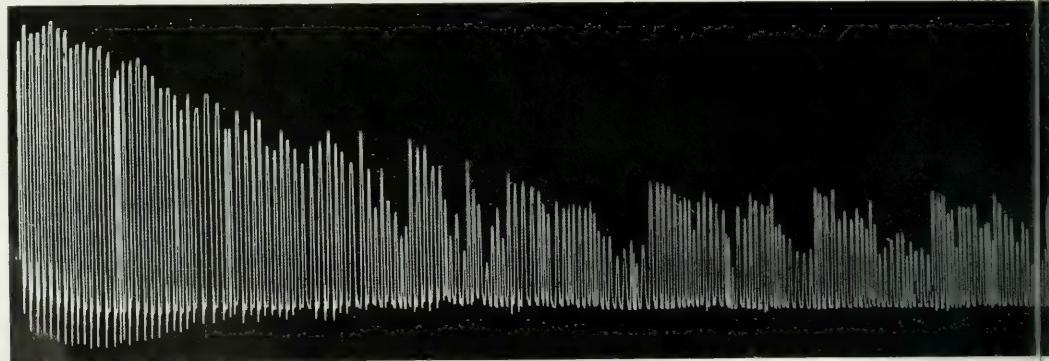


FIG. 2.—Fatigue curve made during hypnosis one hour after completion of Fig. 1. The work was interrupted and the trace of work done under hypnosis.



FIG. 4.—Fatigue curve made during hypnosis within five minutes after completion of Fig. 2. It indicates an increased muscular efficiency during hypnosis even though the subject just indicates the point at which suggestions of renewed energy were made.



3.—Fatigue curve of subject when fully awake, made within three minutes after completion of Fig. 2. It corresponds approximately to the standard fatigue (Fig. 1) and shows the absence of fatigue after work done during hypnosis.



brought to an end because of the limited recording surface of the drum. It demonstrates the much greater amount



of Fig. 3. Experiment concluded when it was clear that the tracing showed  
iously had worked to the limit of his capacity while fully awake. The arrow

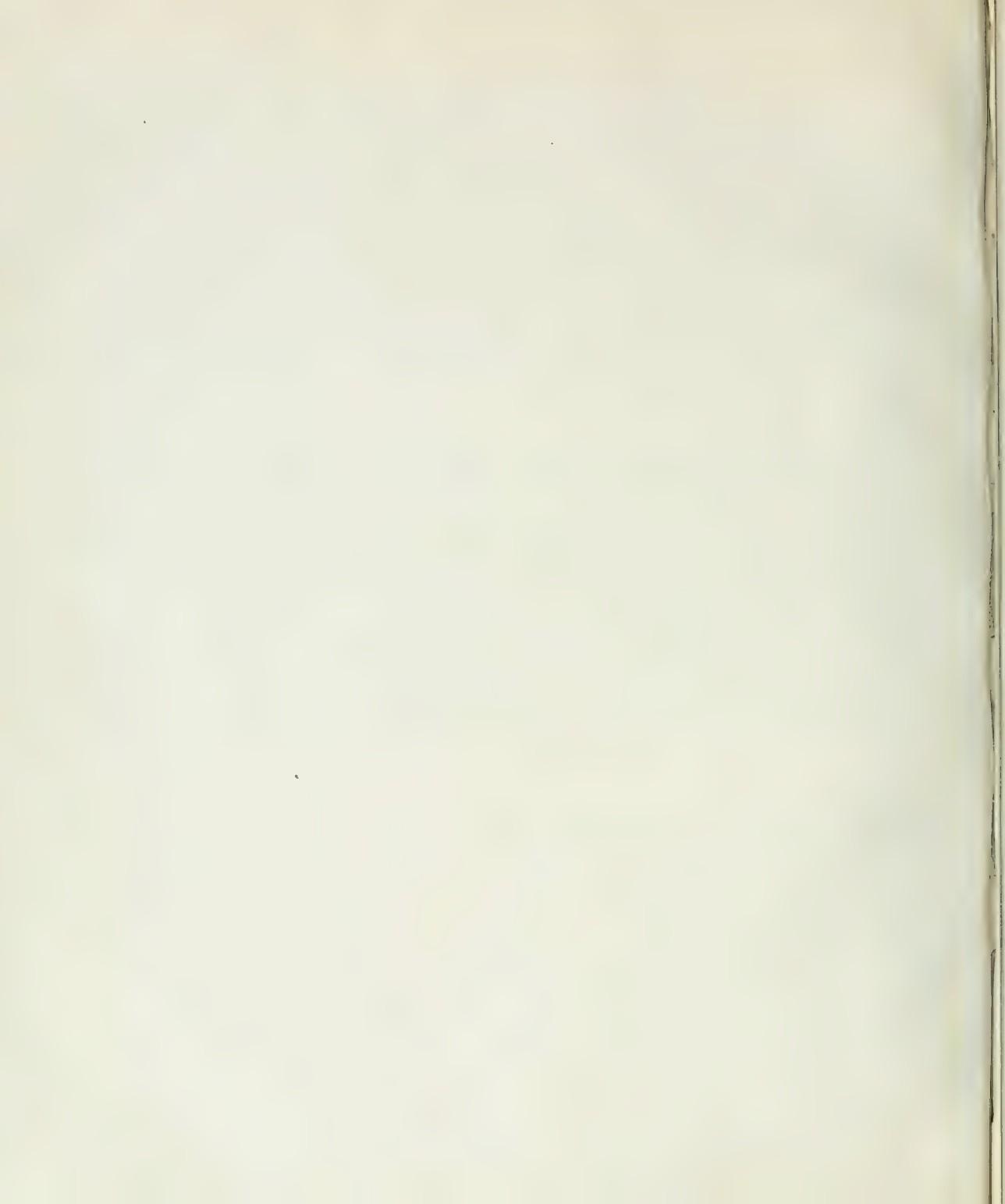






FIG. 5.—In the first half of this tracing (A) the subject is fully awake. The record shows a typical fatigue curve. At the point where it shows the increased work done during hypnosis.

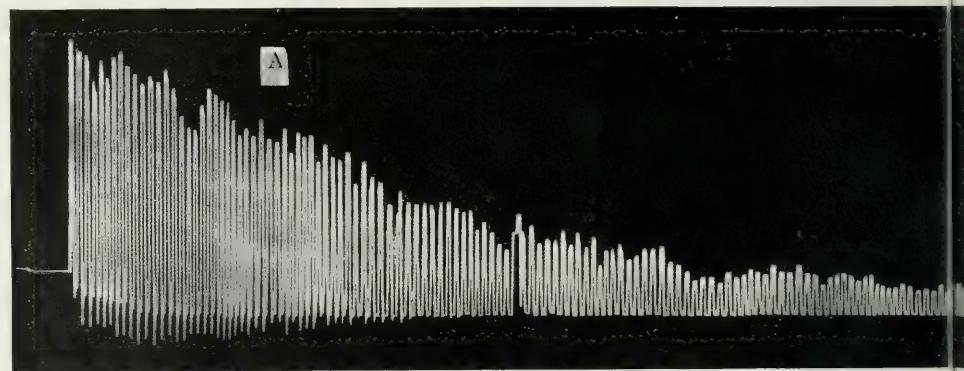


FIG. 6.—In this, as in the previous figure, the subject is permitted to work almost to the point of exhaustion, but the same kind as were given previously during hypnosis. The two arrows indicate the points at which suggestions were marked contrast to that obtained from hypnotic suggestion (Fig. 5).

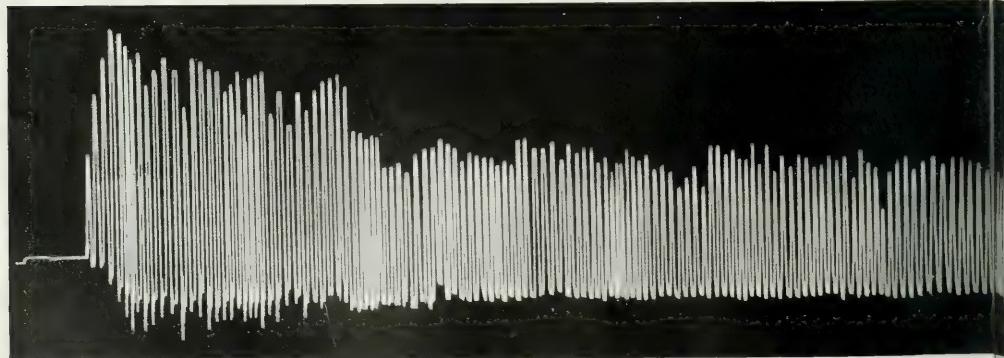


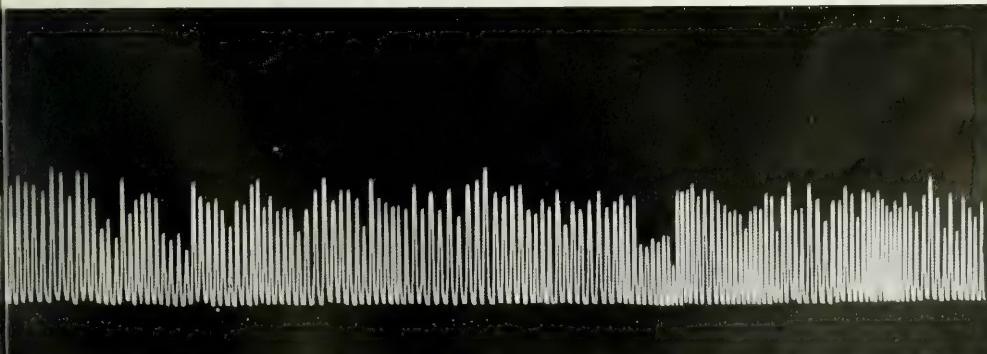
FIG. 7.—A fatigue curve obtained by simply setting the subject to



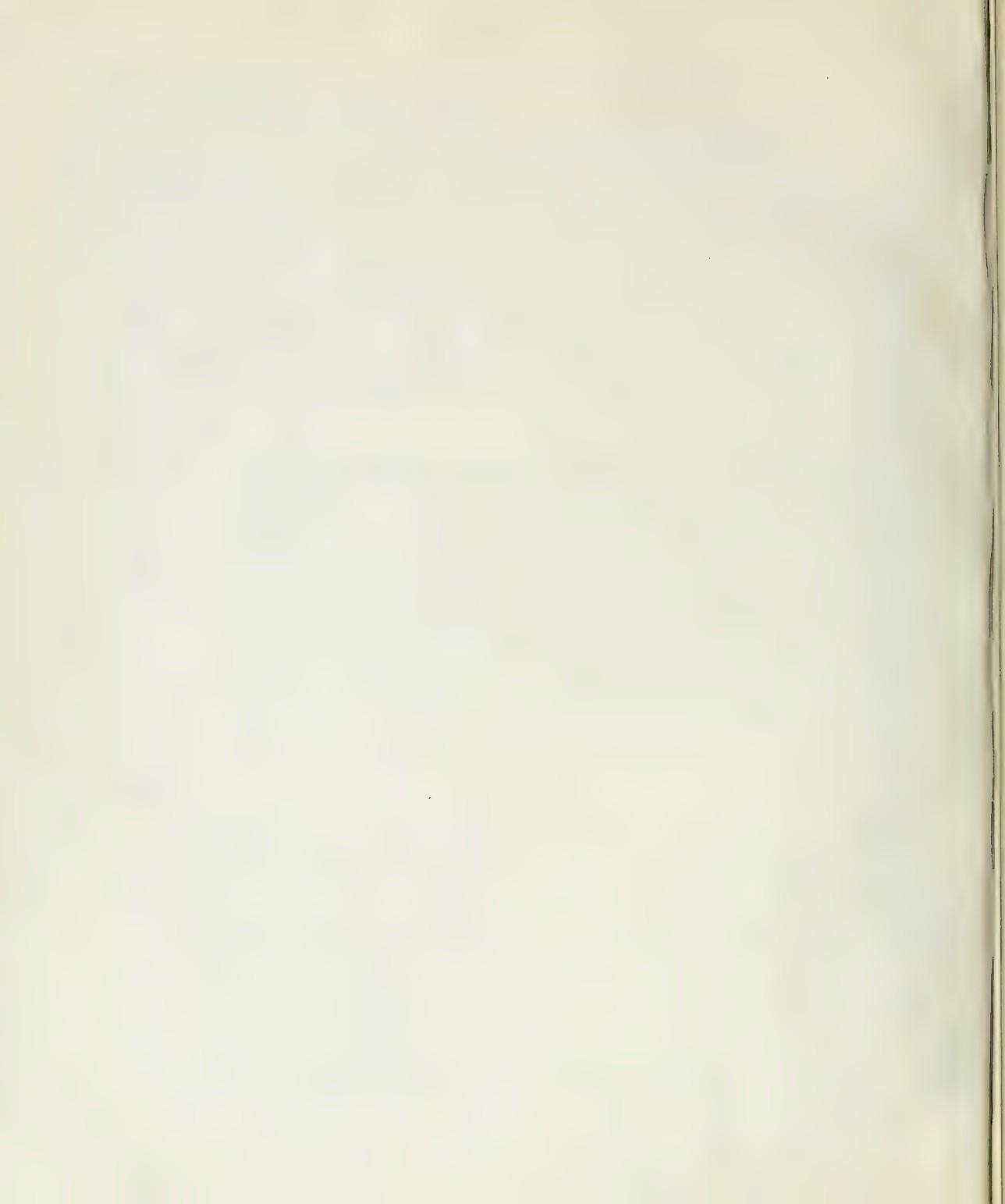
parent that he has about reached the limit of his work capacity he is hypnotized while still working. The second half of the tracing (B)



re in the previous experiment hypnosis is induced, in this experiment suggestions without hypnosis are now given of  
ade. The subject works considerably longer than normally, that is, his endurance is increased, but the curve is in



ork during hypnosis without any suggestions being given at all.



out more emphatically by the fact that the period for recuperation after work in the hypnotic state, that is, the interval necessary for the muscle to make a complete recovery and give a second tracing as extensive as the first, as compared with the recuperative period after work in the waking condition, is startlingly short. Normally, after complete fatigue with a given load a recuperative period of between one and two hours is necessary before a second tracing similar to the first can be obtained. After obtaining a work-curve (Fig. 2) in the hypnotic sleep, however, one can awaken the subject and at once obtain a normal curve of work (Fig. 3) corresponding to the standard work-curve of the waking condition (Fig. 1). One would expect a longer time for recovery after the hypnotic tracing because of the very much greater amount of work done in the hypnotic state. Evidently both subjectively and objectively fatigue in the hypnotic sleep is lessened.

Again and again in the literature the statement is made that suggestions given while the subject is fully awake are as effective as when given during the hypnotic sleep. The records obtained from Experiments IV and V (Figs. 5, A and B; 6, A and B) do not seem to bear this out. In Experiment IV the subject after working almost up to the point of fatigue was hypnotized and given suggestions of increased muscular power. The tracing thus obtained (Fig. 5, A and B) shows several interesting facts: First, that each contraction is at once markedly increased in extent under hypnotic suggestion; secondly, that in extent the contractions tend to equal one another instead of becoming less and less extensive as fatigue comes on, as in the typical waking fatigue curve; and thirdly, that it seems possible to continue to produce such a work-curve indefinitely. In contrast to this the records from Experiment V (Fig. 6, A and B), in which at the point where in the previous experiment the subject had been hypnotized we now gave without hypnosis suggestions of the same kind as had been given previously during hypnosis, show that in this

experiment the contractions do not at once increase in extent nor do they tend to show any improvement as far as extent is concerned; they continue along at about the same level, differing only from the subject's standard fatigue curve in that they are maintained for a longer period of time. In other words, the endurance is increased, but the actual amount of work done is so much greater when the suggestions are given during hypnosis than when given during the waking condition that it would seem reasonable to conclude that suggestions given during the hypnotic sleep are much more effective than the same suggestions given in the absence of hypnosis. Hence, we may say that wherever suggestion is indicated as a therapeutic agent hypnosis should be the method of choice.

As regards the problem which Experiment VI was designed to solve, namely, the effect that hypnosis *per se*, regardless of verbal suggestions, exerts upon muscular work the results were vivified by the fact that this was the last experiment done in the series and, accordingly, it is probable that by the conditioned-reflex mechanism the subject conducts himself exactly as though verbal suggestions were given at this time just as in the previous similar situations. Nevertheless, we present the record obtained (Fig. 7) for what it is worth. It corresponds in general to all of the other records obtained in the hypnotic sleep where suggestions of increased muscular efficiency were given throughout the experiment.

All the results obtained above were controlled by repeating them on the same subject and duplicating them on all the subjects used, seven in all. It is recognized that there are many phases of even this particular problem still untouched, but the results obtained thus far, though fragmentary, justify this preliminary report.

In conclusion I wish to express my thanks to Professors Meyer, Howell and Watson who were ready at all times to give me the benefit of their advice. Dr. Benjamin Sachs rendered helpful assistance in some of the experiments.

## THE GRANULES, VACUOLES AND MITOCHONDRIA IN THE SYMPATHETIC NERVE-FIBERS CULTIVATED IN VITRO

By TAKASABURE MATSUMOTO, M. D., Chiba Medical College, Japan

(From the Department of Embryology, Carnegie Institution of Washington, and The Johns Hopkins Medical School)

### INTRODUCTION

The living sympathetic nerve-fibers are easily cultivated, in saline and other solutions, from explants of the intestine of chick embryos of 4 to 12 days' incubation (Lewis and Lewis, 1912). The fibers extend outward on the under surface of the coverslip and usually form a complicated and irregular network. The larger nerves have a more or less radial direction and are connected by branches which extend between them at various angles.

The material described by Lewis and Lewis consisted in part of specimens fixed in osmic acid vapor and stained with iron-hæmatoxylin. In these preparations the neurofibrils were

found to vary in number in nerves of different sizes and they did not extend into the nerve endings. In places where the fibers were much flattened out the neurofibrils were seen to consist of fine granules. No attempt was made to describe other structures in the fibers. It is now known that it is impossible to distinguish between mitochondrial granules and granules of other origin in material stained with iron-hæmatoxylin. The later application of the so-called vital stains to tissue cultures has opened up new possibilities for the cytologist, and at the suggestion of Dr. Lewis I examined the structure of the living sympathetic nerve-fibers with and without the aid of vital dyes.

#### MATERIALS AND METHODS

Cultures were made in the usual manner. Small bits of the intestine of chick embryos from 6 to 9 days incubation were used. Most of the cultures were grown in Locke's solution plus 0.25 per cent dextrose plus 10 per cent chicken bouillon (Locke-Lewis solution). The nerve-fibers usually appeared in from 10 to 24 hours and often grew out for long distances in 24 to 48 hours. Not all of the explants, however, gave rise to nerve-fibers.

The living cultures were studied both with and without the use of the vital dyes. Neutral red (about 1 to 20,000 in Locke's solution) was used for the granules and vacuoles and janus black No. 2 (about 1 to 10,000 in Locke's solution) for mitochondria. It is very much easier to study the granules and mitochondria after they have taken up these dyes than in the unstained specimens. The living fibers were first examined unstained; then the culture was washed with one or more drops of the neutral red, after which a drop or two of the janus black No. 2 was placed on the preparations and the excess fluid sucked off with a fine pipette. Sometimes the neutral red and janus black No. 2 were made up together in the same solution, or the janus black No. 2 was put on the specimen before the neutral red. The neutral red was taken up in a few seconds by the granules and vacuoles, while the janus black No. 2 required several minutes to color the mitochondria.

#### OBSERVATIONS

The nerve-fibers in explants from 6-day embryos resembled those from the older ones described in more detail farther on. The mitochondrial rods and granules were irregularly arranged, except that they were more often at the periphery of the fibers than in the central part. The rods had their long axes more or less parallel to that of the fiber. Some of them moved a little, usually up or down the fiber. The granules which took up the neutral red, when present, were scattered and few in number. A few colorless vacuoles which did not take up neutral red were also found along the fibers and in the nerve endings.

A typical fiber in a 48-hour culture from a 7-day chick embryo, shown in Fig. 1, contained a few scattered, rod-shaped mitochondria along the periphery of the nerve stem. In the branching nerve endings they were granular in form and situated, for the most part, in the small nodes from which delicate lateral branches were given off. In this particular fiber most of these small nodes had one mitochondrion, a few showed two or three. Mitochondria were also scattered in places on the branches between the nodes. There were no neutral red granules or vacuoles in this part of the nerve and no indications of neurofibrils were to be seen.

In another 48-hour culture of a 7-day chick embryo (Fig. 2), a somewhat different condition existed. There were very few mitochondria along the fiber and these had no definite relation to the periphery. The slightly expanded ending contained numerous mitochondria in the form of granules and short rods and such mitochondria were present also in the two principal branches. There were no indications of neurofibrils. In

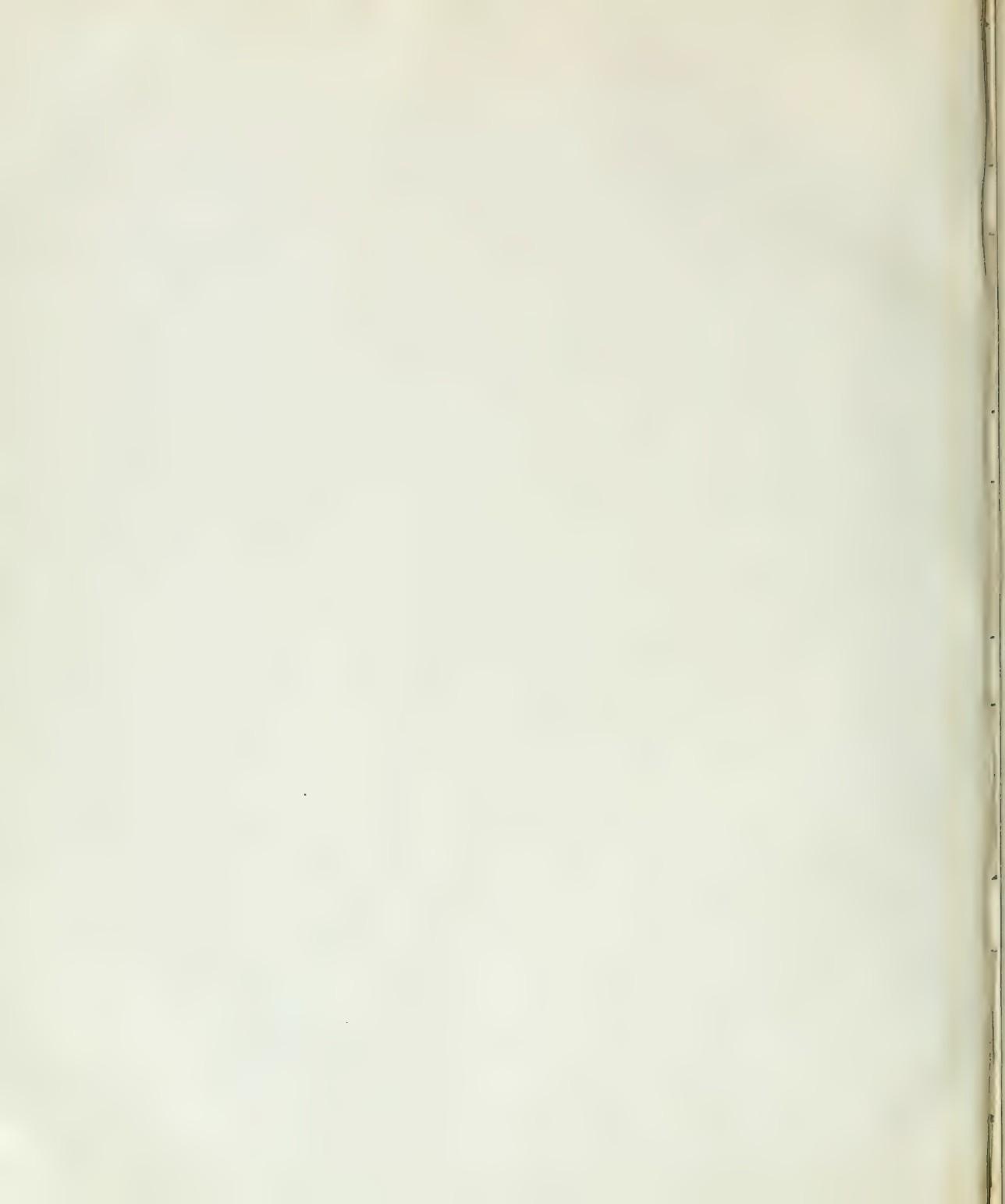
another similar culture the larger nerve trunks, as a rule, possessed many rod-like mitochondria arranged with their long axes more or less parallel to the long axis of the fiber (Fig. 3). The smaller branches and nerve endings in this same culture contained fewer mitochondria than did the larger trunks (Fig. 4). Only a few scattered granules had taken up the neutral red. No indications of neurofibrils were observed. In some fibers which lived 4 days there was no noticeable increase in the number of granules or vacuoles which take up the neutral red, such as usually occurs in the mesenchyme cells. This may be due to the fact that in the case of the nerve-fiber we are dealing with a process of the cell and not with the cell body. In addition to the neutral red vacuoles, which were not numerous, some of the fibers and endings contained clear, unstained vacuoles. These were evidently different from the vacuoles which take up the neutral red, since they were often side by side, yet one type took up the red while the other did not.

The cultures from 8-day embryos were similar to those from the 7-day ones. The nerves contained mitochondrial rods and granules which varied in number in different fibers and in different nerve endings. In some they were numerous, while others contained only a few. As in the cultures from 7-day chicks, the rod-shaped mitochondria had their long axes parallel to the long axis of the fiber and did not form definite chains or rows. The mitochondria were more numerous in the larger nerve stems than in the smaller ones. The number of granules which took up neutral red varied greatly in different fibers and in different nerve endings. In the 24-hour cultures they varied as much and did not seem to be any less numerous than in the 3-day cultures. Some of the nerve endings in 3-day cultures were devoid of any of the granules or vacuoles which take up the neutral red, or contained, at most, only one or two (Fig. 5). Sometimes, even in the 24-hour cultures, there were more neutral red granules than mitochondria. Many of the fibers and endings, as in the cultures from the 7-day embryos, contained large unstained vacuoles (Fig. 5). These seem to be more common in cultures from older embryos than in those from younger ones and were found in the 24-hour growths as well as in the older ones.

In addition to the distribution of mitochondria and granules in the fibers and nerve endings, there was usually to be found a marked accumulation of granules and vacuoles in the larger nodes of the nerves, as shown in Figs. 6 and 7. These nodes consist of a mass of granules and small vacuoles which take up the neutral red. This mass is on the peripheral side of a clear area; on the proximal side of this area there may be a few granules. The large mass of neutral red granules and vacuoles has sometimes a more or less clear area at its center. The nodes have the appearance of a degenerating cell with a mass of granules and vacuoles about a centrosphere which lies at one side or at one end of a clear area—the nucleus.

In cultures from 9-day chick embryos there was as much variation in the number and arrangement of the mitochondria and granules as in those from younger embryos. One cannot distinguish the living nerve-fibers in the cultures of 9-day





embryos from those cultivated from a 7-, 8-, or even a 5- or 6-day embryo.

#### THE MITOCHONDRIA

In none of the fibers and nerve endings examined was there any suggestion of a regular distribution of the mitochondria, such as one would expect to find if they are to give or are giving rise to neurofibrils. Moreover, no neurofibrils were seen in the living fibers.

Neurofibrils were described by Lewis and Lewis (1912) in fixed cultures of the same ages and length of growth as the ones examined in this study. The fact that neurofibrils were not seen in the living fibers is no proof that they were not there; on the other hand, the fact that they can be seen in similar fibers, when fixed and stained, is no proof that they exist in the living, for they may very well be coagulation products.

Although the distribution of mitochondria varied both in number and position there was more or less regularity in their orientation, especially in the fibers where the rods and short threads usually had their long axes parallel with the long axis of the fiber. One might argue that this peculiar orientation was caused by the presence of invisible neurofibrils. On the other hand, it might equally well be due to some sort of a molecular or metabolic arrangement of the cytoplasm. The mitochondria show a moderate degree of movement. We have no method of determining whether this is passive, due to cytoplasmic changes, or active, on the part of the mitochondria. The movements are slower and differ in character from those of the granules which take up the neutral red. The mitochondria seem to be more numerous in the larger nerve-fibers and in the regions nearer the explant.

#### THE GRANULES

The granules which take up the neutral red varied greatly in size and number, being irregularly distributed along fibers and endings. The larger nodes, however, especially half, were crowded full of them. The granules usually exhibited considerable movement, especially in a longitudinal direction along the fiber and at the periphery. They moved more rapidly than the mitochondria and over longer distances, sometimes in a jerky manner.

The granules did not seem to have any definite orientation nor were they increased in number in the older cultures. Their significance is unknown, but it is not unlikely that they are degeneration granules, such as those described by Lewis (1919) in fibroblasts. Vacuoles which take up neutral red were rarely observed except in the larger nodes.

#### DESCRIPTION OF PLATE<sup>1</sup>

FIG. 1.—Sympathetic nerve and branched ending with mitochondria. 48-hour culture from intestine of 7-day chick embryo.

FIG. 2.—Sympathetic nerve and ending with mitochondria and a few granules and vacuoles which take up neutral red. 48-hour culture from intestine of 7-day chick embryo.

FIG. 3.—Large sympathetic nerve with many mitochondria and granules. 48-hour culture from intestine of 7-day chick embryo.

FIG. 4.—Nerve ending from nerve shown in Fig. 3, with mitochondria and granules.

FIG. 5.—Nerve ending with mitochondria and large vacuoles which do not take up neutral red. 3-day culture from intestine of 8-day chick embryo.

FIG. 6.—Node on sympathetic nerve with a large mass of granules and vacuoles, which take up neutral red, a few fat globules and a clear area. 5-day culture from intestine of an 8-day chick embryo.

FIG. 7.—Somewhat similar node. 3-day culture from intestine of 8-day chick embryo.

<sup>1</sup> The figures are all free-hand drawings from living cultures to which neutral red and Janus black No. 2 were added after the culture had grown out. The blue-black mitochondria of the living are represented in black and the granules and vacuoles, which take up the neutral red, in grey.

#### BIOGRAPHY OF SIR WILLIAM OSLER

Lady Osler has requested me to prepare a biography of her husband, and I will be most grateful to anyone who chances to see this note, for any letters or personal reminiscences, or for information concerning others who may possibly supply letters.

Copies of all letters, no matter how brief, are requested, and if dates are omitted it is hoped that they may be supplied if possible.

If the originals are forwarded for copy they will be promptly returned.

HARVEY CUSHING, M. D.,  
Peter Bent Brigham Hospital,  
Boston, Mass.

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## VENOUS THROMBOSIS, PULMONARY INFARCTION AND EMBOLISM FOLLOWING GYNÆCOLOGICAL OPERATIONS

By H. H. HAMPTON and LAWRENCE R. WHARTON

(From the Gynaecological Department of The Johns Hopkins Hospital)

### INTRODUCTION

Since Virchow's monumental work, thrombosis and embolism have held the attention of pathologist, internist and surgeon, and, as a result, a vast amount of literature has accumulated. Our personal interest was aroused recently by several consecutive deaths from pulmonary embolism, constituting 50 per cent of our fatalities for the past year. It was quite evident from the onset that prevention of embolism in our clinic, if attainable in any degree, would depend upon an accurate study of our cases of phlebitis and thrombosis. We have therefore collected statistics embracing all the cases of phlebitis and thrombosis that have occurred since the opening of our clinic in 1889. About 40 of these cases have been previously reported in excellent papers by John G. Clark<sup>1</sup> and by Benjamin R. Schenck.<sup>2</sup>

We had been engaged in compiling our statistics but a short while when we made the observation that, in the case of many patients with phlebitis who later developed pulmonary complications, a diagnosis of pleurisy or pneumonia had been made without any reference to the possibility of infarction.

We noticed, moreover, that a certain number of our patients who had suffered from an unrecognized pulmonary infarction died later of pulmonary embolism.

The second half of our paper, therefore, we shall devote to the pulmonary complications associated with venous thrombosis. In doing this we shall attempt to show that these conditions have often been overlooked and shall present the clinical data on the basis of which we think they may be recognized. We are presenting these subjects entirely from a clinical viewpoint, having conducted no experiments upon either thrombus formation or infarction. We have made rather free use of the literature, however, and in practically all of our fatalities fortunately have been able to check our clinical findings by post-mortem examinations.

### POST-OPERATIVE VENOUS THROMBOSIS

#### THE PATHOLOGY OF THROMBOSIS

Among pathologists, Dr. William H. Welch<sup>3</sup> stands out pre-eminently for his broad vision of the whole subject. In

preparing this paper, we have liberally used his article, which is to be found in "Allbutt's System of Medicine."

What are the factors concerned in the production of thrombosis? Following the classification of previous observers we might conveniently bring them under two heads—*primary* and *contributory*. Under *primary* we would place infection and trauma, and under *contributory*, slowing of the blood stream, chemical and physical changes in the blood and anatomical relations of the blood-vessels.

We can no more attribute all cases of thrombosis to a single cause than we can the failure of a corn crop. The crop failure may be due to drought, lack of fertility, parasites, poor cultivation, or to all these conditions working together. So with venous thrombosis; there is practically always more than one single etiological factor to be considered. In a case of phlegmasia alba dolens very few will deny that infection plays the major rôle. In the occurrence of thrombosis following a clean abdominal operation, however, it is rather hard to draw an indictment against infection.

The process of thrombus formation has been studied extensively by many pathologists. It is practically agreed that the thrombus is first represented by a collection of blood-platelets; in a few minutes leucocytes and fibrin are added to the picture. The thrombus may be described as leucocytic or fibrinous, depending upon which of these two elements dominates. Of this much we are fairly certain; but when we make inquiry as to what induces the endothelial injury that causes the collection of platelets and leucocytes, we are broaching a question that is still open. Is it the presence of traumatism, toxins or actual bacterial invasion? All these questions must be answered upon sound experimental evidence before we arrive at a clear understanding of thrombus formation.

Even without this knowledge, however, on the basis of clinical observation we have a certain right to speculate as to the principal causes of this condition. We do know that patients come to us in the pink of condition, have clean laparotomies and yet develop thrombosis of the leg veins. We are naturally justified in assuming, therefore, that operation has furnished all the necessary conditions for the development of thrombosis. This complication is not peculiar to any single type of operation, although it is most common after a laparotomy. What factors conducive to thrombosis, then, are common to all operations? Traumatism of the tissues is certainly one; furthermore, we believe it is generally agreed that there is no such thing as an operation without the introduction of organisms.

The important part that operative procedures play in the production of thrombosis is readily seen by a glance at that group of cases in which thrombosis is most often found—myomata of the uterus. We are reporting 69 cases of myoma in which thrombosis developed after operation. Of these patients 17 per cent were anæmic, 24 per cent were suffering from infections in the fallopian tubes, and a large number had pelvic congestion with dilated veins and lymphatics. These are the conditions that are supposed to favor thrombus

formation. Yet only one patient out of the 69 had developed thrombosis prior to the operation. This seems to indicate that the operation furnished the conditions necessary to thrombus formation.

What is there peculiar to a hysterectomy for myoma that contributes to thrombosis? The abdomen is usually opened through a long midline incision. The tumor is delivered by sharp dissection through an area almost free from blood-vessels. The edges of the wound in the abdominal wall are protected from infection by wet gauze. In all hysterectomies we clamp large vessels, sutures at times break and are replaced. It is sometimes difficult to be sure that vessels are not traumatized proximal to the point of ligature. A certain number of myomata extend into the broad ligaments and when enucleated leave behind a large raw bed of traumatized tissue. The vaginal vault, moreover, is richly supplied with large venous plexuses, which in multiparae are often tortuous and varicose. In low cervical amputations and in all pan-hysterectomies, these vessels must be cut and ligated. During the release of the bladder from its uterine attachments, another large vascular area is handled. All these procedures involve trauma and the possibility of subsequent thrombosis.

Infection, also, has an open door here. In hysterectomies the cervical canal or vaginal vault is always opened. The fallopian tubes, moreover, often harbor old chronic inflammatory processes. In all probability the cervical canal, the vaginal vault and the fallopian tubes form the usual portals of entry for organisms. It does not seem unreasonable to suppose that here should be a potential source of infection, when to the normal flora we have added the possibility of secondary contamination in the presence of traumatized tissue.

Here, then, we have a fertile field for the development of thrombosis—traumatized tissue and blood-vessels in the presence of organisms. It seems, therefore, that infection and trauma to the pelvic vessels are concerned in the great majority of cases of post-operative thrombosis. We cannot agree with Clark that most cases of femoral thrombosis develop from the inferior or deep epigastries; nor does the evidence obtained from the autopsy table seem to support this contention. It may be, however, that some thromboses following the Gilliam suspension of the uterus have their origin in the manner that Clark has described.

Why is thrombosis more common in the left than in the right leg? The anatomical differences in the return circulation of the two sides are always cited by way of explanation, but the many unsuccessful attempts to answer this question merely serve to remind us that we do not yet understand all the conditions favoring venous thrombosis.

*Prophylaxis.*—We hoped to plot a curve that would show a decrease of thrombosis as the technique of the operating room improved. This was so irregular, however, that nothing could be derived from it. During the last three years there has been a marked decrease in the number of these cases.

It seems that our only hope for reducing the frequency of this complication lay in the constant care of details during the operation, the gentle handling of tissues and the use of sharp dissection wherever possible. Examination of the legs for thrombosed or varicosed vessels should always be made before operation. The legs should not be bound too tightly with straps. We cannot see any harm from the use of the Trendelenburg posture wherever necessary. In laparotomies care should be exercised in using deep or heavy retractors. In spite of the fact that we have used this precaution systematically, the examination of the peritoneum over the region of the iliac vessels not infrequently has shown evidence of traumatism. We agree with the Mayos<sup>4</sup> in getting our patients out of bed early. In letting up a patient that has an unexplained temperature, however, we feel that one should proceed cautiously.

*The Clinical Aspects of Thrombosis.*—The cases of thrombosis which we present occurred after operations performed between the years 1890 and 1918 inclusive. During this period of almost 30 years, about 21,000 patients were operated upon in the gynaecological clinic. In this number are included all types of operations, both perineal and abdominal. During this period there have been 205 cases of femoral thrombo-phlebitis; in other words, the incidence of thrombosis following all types of gynaecological operations is about 1 per cent. This agrees closely with the results in other clinics. Klein,<sup>5</sup> of Vienna, reported, in 1911, 70 cases of thrombosis following 5851 operations, a frequency of 1.2 per cent. Franz<sup>6</sup> found an incidence of 1.8 per cent. Bondy<sup>7</sup> in 1000 gynaecological operations and Ranzi<sup>8</sup> in 6871 cases reported 1.3 per cent and 1.2 per cent respectively.

In an almost overwhelming majority of our cases thrombo-phlebitis occurred after a laparotomy. Of our 205 cases of thrombosis, 81 per cent followed abdominal operations, 31 per cent supravaginal hysterectomy, 11 per cent panhysterectomy, 16 per cent operations on the adnexa, 10 per cent suspensions of the uterus, 5 per cent myomectomy, 8 per cent some perineal operation. Klein reports that 56 per cent of his 70 cases occurred after laparotomy.

Of our 205 patients, 69 were operated upon for myomata of the uterus. This constitutes by far the largest single group. In association with post-operative thrombosis, 34 per cent of our series of thrombosis followed myoma operations—in 8 per cent the myomata were complicated by salpingitis and were primarily infected cases. Next in importance to myomata comes the group of salpingitis, pyosalpinx and similar infections of the fallopian tubes. Fourteen per cent of our cases of thrombosis followed some operation done to relieve this condition. Ovarian cysts almost equal the group of inflammatory conditions in the incidence of thrombosis, for 13 per cent of our thromboses were associated with the removal of cystic tumors of the ovary. Six per cent followed panhysterectomy for carcinoma of the cervix; 1 per cent carcinoma of the fundus; 7 per cent suspension of the uterus; 8 per cent perineal operations, and 4 per cent appendectomies.

The remaining cases of thrombosis were divided in an almost equal ratio among operations on the kidneys, gall-bladder, extra-uterine pregnancy, vesico-vaginal fistula and rectal operations.

From this comparison it is clearly evident that venous thrombosis and the removal of large pelvic tumors, particularly myomata and ovarian cysts, are closely associated. This has been a matter of common observation among gynaecologists for some time. According to statistics on this subject, it is practically certain that in 100 hysteromyomectomies from three to five of the patients will develop the clinical signs and symptoms of thrombophlebitis of the leg. Kelly and Cullen<sup>9</sup> noted that thrombosis followed hysterectomy for myoma in 3 per cent of their cases; Klein reported 3.3 per cent in 730 myoma operations; Zurhelle,<sup>10</sup> 2.7 per cent; Bruckhard,<sup>11</sup> 4.6 per cent in 236 operations. The endeavor to explain the heavy incidence of thrombosis following myoma operations has evoked many speculations. These are discussed in another part of this paper.

Strassmann and Lehmann<sup>12</sup> laid great stress on changes in the cardiac musculature in myomata. They claimed that in 40.8 per cent of all cases of myomata they were able to find a cardiac lesion, and called this syndrome the "myoma heart." Klein seems to support this view. Unfortunately, we cannot see that there is any such direct connection between the cardiac musculature and myomata of the uterus. Although we have seen many patients suffering with myomata who also showed pronounced symptoms referable to cardiac insufficiency, our experience would indicate that these symptoms are almost always due to concomitant factors which of themselves would increase the load of the heart, such as prolonged secondary anaemia due to persistent uterine bleeding over a long period of time, the venous congestion incident to a large intra-abdominal mass, the additional body weight of a parasitic tumor and the poor general condition of some of these patients. These factors, we believe, are sufficient to account for most of the cardiac symptoms seen in myoma cases.

Furthermore, in 19 autopsies performed on patients dead of pulmonary embolism following venous thrombosis after pelvic operations, 10 of which were hysterectomies, there were no cardiac changes which could support the view of Strassmann and Lehmann. In several of these cases, moreover, the myomata were as large as one usually finds. Kelly and Cullen have investigated this subject in an exhaustive manner and have expressed their views in the large volume on "Myomata of the Uterus," published in 1906. Their conclusions and ours are essentially the same, both arrived at independently.

*The Vessels Involved in Thrombosis.*—In almost all writings on this subject, the frequency of thrombosis of the veins of the left leg has been emphasized. This fact is very evident in the present group of cases, where in 66 per cent the vessels of the left leg were involved, in 24 per cent of the right and in 9 per cent of both legs. In one instance the vessels involved were in the left arm, in another the superficial veins of the neck and in a third the mesenteric veins.

In the left leg the vessel usually involved was the femoral vein (40 per cent), the left saphenous in 12 per cent and the left popliteal in 2 per cent. In the right leg the femoral vein was involved in 10 per cent of the cases and the saphenous in 7 per cent.

In all of these instances the thrombosis was clinically evident from characteristic signs and symptoms. At the autopsy table, however, in patients dead of pulmonary embolism, thrombosis is discovered in places, rendering the diagnosis much more difficult, as, for example, in the veins of the pelvis. As a result of our study of the clinical picture of thrombo-phlebitis, we have been led to believe that many cases of unexplained post-operative elevation of temperature, particularly those occurring during the second and third weeks of convalescence, may be due to phlebitis and thrombosis of some of these venous trunks which are so situated as not to cause a clean-cut clinical picture and which are usually recognized only on the autopsy table casually or in the search for the source of a fatal pulmonary embolus.

With the view of determining, if possible, any factors predisposing to phlebitis or thrombosis, we have studied our cases from various aspects—the pre-operative condition, the type of operation done, the indication for drainage, the relation of previous pregnancy, the age of the patients and the time of operation. The pre-operative condition of these patients on the whole was satisfactory. Two-thirds of them were in good condition, were well nourished and without any elevation of temperature; 13 per cent were in fair condition; 15 per cent were anaemic, with a haemoglobin of less than 65 per cent, while only 8 per cent were clearly poor surgical risks. Of all these patients only 28 per cent had a temperature of 99° or higher on admission. Eighty-one per cent were married; 19 per cent single; 73 per cent parous; 27 per cent nulliparous, the sterility being due usually to myomata or salpingitis. Seventy-seven per cent were "clean" cases, 23 per cent were infected cases from the beginning; 33 per cent were drained at operation and 67 per cent were not. The ages were equally divided between 20 and 50, with a very few cases beyond each limit. Whether there is any association between any of these data and thrombosis remains doubtful.

*The Clinical Picture of Thrombosis.*—The clinical picture of thrombosis is too well known to require or merit much attention. Matters of common knowledge will be merely mentioned. There are one or two points, however, which, according to the literature, seem rather confused, and with regard to these we shall give our results in greater detail.

The first item of interest in our cases of thrombophlebitis is that practically none of the patients showed an absolutely normal convalescence up to the onset of the clinical manifestations of thrombosis. The one point of variance from the normal was in the temperature curve.

In the usual post-operative convalescence in a clean case, we expect the temperature to reach normal and remain there by the end of the first week, or certainly during the second week. In our cases of thrombosis, this is not the rule; in

fact, it is clearly the exception. Almost without exception our patients have shown a definite, low, persisting pyrexia from shortly after the time of operation until the onset of pain and swelling of the leg, during a period when the temperature should clearly be normal. This temperature is usually not high; its most frequent variation is from 99° to 100°F. With this low fever the pulse usually remains low, the pulse curve either accompanying or falling below the temperature curve.

Michaelis<sup>13, 14</sup> has been one of the few and also one of the earliest observers to call attention to this point. He goes so far as to state that in patients who have a perfectly normal temperature curve after operation, thrombosis and embolism do not need to be feared. Michaelis has been contradicted by Küster,<sup>15</sup> who failed to notice this premonitory rise of temperature. G. Petré<sup>16</sup> came to the conclusion in 1913 that in a majority of his cases this low febrile course was noted without other symptoms and like Michaelis believes it is of some value in warning one of the possible presence of an obscure thrombophlebitis. Mahler<sup>17</sup> stated that there was a premonitory rise in pulse before the thrombosis became evident, but that the temperature remained absolutely normal.

Some of these observers doubtless have been dealing with groups containing both post-operative and puerperal thrombosis, so that those which we are considering here may not be precisely similar. As regards post-operative thrombosis, however, on the basis of our findings in 205 cases, we believe we can affirm that the large majority of the patients have a persistent, low, unexplained elevation of temperature before the clinical evidence of the thrombosis becomes apparent. In such cases we believe the possibility of obscure thrombosis and subsequent infarction or embolism should always be kept in mind.

*Signs and Symptoms of Thrombosis.*—The symptoms of peripheral thrombosis are usually unmistakable. Pain is almost always the first complaint of the patient, and is usually the first symptom explanatory of the low fever. In rare cases, tenderness may be present along the course of the femoral vein before the onset of pain. The pain is sometimes very acute, requiring morphin, and is usually rather persistent, according to the severity of the thrombosis.

Swelling usually follows promptly and may be marked. It is limited to the region supplied by the vein thrombosed; in saphenous thrombosis, to the ankle and lower part of the leg; in popliteal, to the whole lower leg; in femoral, to the leg and thigh. Elevation of the surface temperature is common. Redness over the course of the vein is rather unusual; the limb occasionally becomes cyanotic.

It is well to remember, however, as Welch has pointed out, that thrombosis of large vessel may be present with almost no swelling. This finding we have verified at autopsy both in regard to the femoral and saphenous veins, and on this basis can state that thrombosis of a large peripheral vein may be present without any local signs or symptoms whatever.

The temperature does not rise decidedly until the initial symptom of pain has become evident; in fact, there is usually

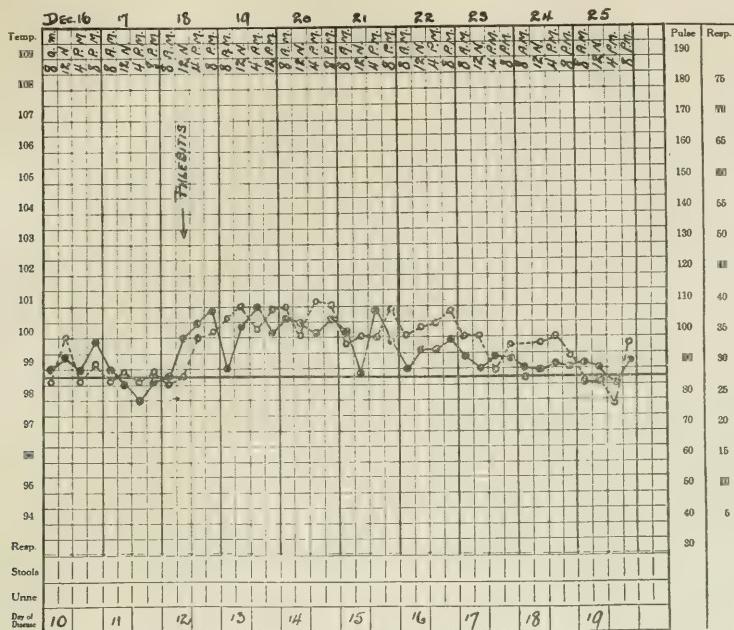


FIG. 1.—Temperature curve. Femoral thrombo-phlebitis, appearing on the twelfth day after operation. Gynaecological No. 20792. The dots and solid lines indicate the temperature; rings and dashes indicate the pulse.

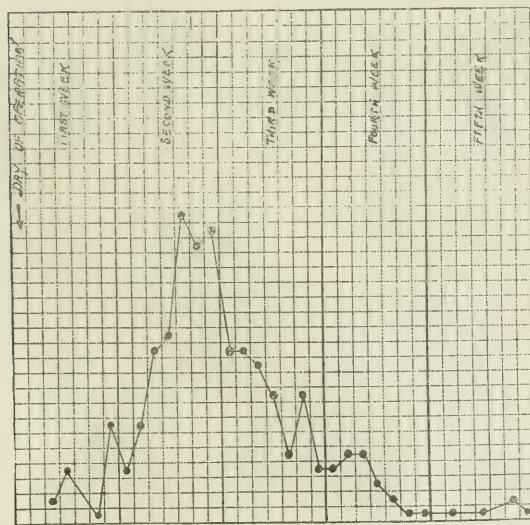


FIG. 2.—Curve of incidence of post-operative femoral thrombo-phlebitis, based on a series of two hundred and five cases.

no marked rise until 24 hours after the onset of pain. It may or may not precede the swelling. There is usually no marked increase in the pulse rate, except in cases showing a very high temperature or pulmonary complications.

In every case that we have observed, the temperature during the course of the clinical manifestations of the thrombosis was 99° F. or over. Furthermore, in 70 per cent of our cases the temperature during the thrombosis rose to a higher point than it did during the first post-operative elevation. This has been an outstanding characteristic in all our cases. A typical temperature curve is shown in Fig. 1.

Most of the thromboses occurred during the second and third weeks of convalescence. The most common period is at the end of the second week, as is shown in our graphic curve of incidence. About 30 per cent of all of our cases of thromboses became evident in the 72 hours of the 12th, 13th and 14th days.

Pain is the first symptom to appear and also the first to disappear. Swelling follows the same rule and being the last symptom to appear, is also the last to depart. The convalescence of the patients is greatly prolonged by thrombo-phlebitis. The average stay in the hospital of these patients was 39 days, which is much longer than normal.

In spite of this prolonged convalescence, 63 per cent of our patients had symptoms referable to their thrombosis when discharged from the hospital. In most of these cases the symptom was swelling of the leg. In some instances, as is well known, this swelling persists for months.

*Pulmonary Complications of Femoral Thrombosis.*—The most serious complications of thrombophlebitis are pulmonary. In our series of 205, 14 patients (7 per cent) developed pulmonary infarcts, and three patients (1.5 per cent) pulmonary embolism. There were two deaths in this series, one patient dying of lung abscesses that developed in pulmonary infarcts, another of pulmonary embolism. Autopsies confirmed the presence of the thrombosis, infarction, lung abscesses and embolism. Two of the three patients with pulmonary embolism recovered, although the attacks were so grave as to be almost fatal.

As far as life is concerned, post-operative thrombophlebitis of the veins of the leg does not seem to be as serious as that of the pelvic vessels. This observation has been made before. In fact, it has become almost axiomatic that, of all types of post-operative thrombosis, that involving the femoral and saphenous veins is the most benign, particularly when accompanied with pain and swelling. The infrequency of death from pulmonary embolism in this type of thrombosis is indeed a remarkable fact.

The relatively benign course of this type of thrombosis has led some observers to draw rather sweeping conclusions. One reliable writer has stated that pulmonary emboli never have their origin from the saphenous vein. Such statements as this we cannot accept without reservation. Our own autopsy records, together with those of other clinics, show conclusively that fatal emboli may have their source in either the saphenous

or femoral vein, in cases where there is pain and swelling of the leg as well as in those in which these clinical symptoms of thrombosis are absent. The fact remains, however, that fatal pulmonary embolism is not often associated with clinically evident thrombosis of the veins of the leg.

*Pulmonary infarction* is a more frequent complication of thrombosis than pulmonary embolism. In 7 per cent of our cases of thrombosis infarcts developed. That particles of thrombi are broken off and washed into the general circulation is evident from these statistics. Why they are rarely large enough to cause death from embolism is a rather difficult question to answer. The fact that we have kept all patients suffering from thrombosis in bed for a long period of time may perhaps have something to do with the infrequency of the development of embolism.

The treatment of thrombosis is very simple, chiefly because there is very little one can do. Twenty-five years ago the application of strong counter-irritants was in vogue. Legs were painted with iodine from Poupart's ligament to the heel. Then came the era of ichthyol and lead and opium liniments. In recent years our methods of treatment have become progressively simpler. We have discontinued local applications, as there may be danger in applying them too vigorously. Ice bags may be used locally, precaution being taken not to cause ice burns. Elevation of the leg will help the return flow of blood and ease the discomfort. Sedatives are indicated for the pain. We keep these patients in bed until the pain has disappeared and the swelling has practically subsided. It may not be superfluous to insist that massage in the treatment of post-operative pain in the legs is a dangerous procedure until the cause of that pain is known.

#### PULMONARY INFARCTION AND EMBOLISM

While we were studying the cases of post-operative thrombosis, our attention was attracted by the fact that a certain number of these patients developed pulmonary complications which to us clearly seemed to be due to infarcts. We noticed, moreover, that very few of these cases were diagnosed as pulmonary infarction; as a rule, they were called pleurisy or pneumonia. It therefore occurred to us to collect the cases diagnosed as post-operative pleurisy and see how many of them were primarily pleurisy and how many were infarctions. We did the same with the cases diagnosed as post-operative pneumonia, bronchopneumonia and bronchitis. And from the material collected in the study of 40 cases diagnosed as post-operative pleurisy, 80 cases as post-operative pneumonia and bronchopneumonia, and 50 cases as post-operative bronchitis, we have picked out 34 cases of undoubtedly post-operative pulmonary infarction. This number probably does not include all the cases we have had, for we have consistently eliminated all cases in which for any reason whatever the data were not sufficient to make a clean-cut diagnosis.

The study of infarctions of the lung naturally led us to include pulmonary embolism, for, in spite of essential differences, the two groups of cases are so closely associated as to

be inseparable, both clinically and pathologically. And both are likewise related to thrombosis. Thus we have seen cases of recognized clinical thrombosis repeatedly give rise to pulmonary infarction and attacks of infarction diagnosed as pleurisy and pneumonia followed later by fatal pulmonary embolism. Furthermore, without the information gained by the post-mortem examination of cases of pulmonary infarction and embolism, many clinical conclusions whose validity we have come to regard with some degree of assurance would hardly pass beyond the pale of impressionistic deductions.

The question naturally arises at this point: Why should the diagnosis of post-operative pulmonary infarction be so often missed, and on what basis do we feel warranted in assuming to question the diagnosis of other men—we who have never seen the patients and are merely looking over the records of these cases 10 to 25 years after the patients have left the hospital? After we have presented the cases of this series, we shall try to answer these pertinent questions.

The pulmonary complications associated with post-operative thrombosis fall into two main groups—pulmonary infarction and pulmonary embolism. A considerable amount of confusion has resulted from using these terms interchangeably. To avoid this, we shall roughly define these terms as we intend to use them. By infarction we mean the pathological and clinical picture following the dislodging of a thrombus, not large enough to occlude the blood supply of an entire lobe, but sufficient to occlude the artery supplying part of a lobe, giving rise to the characteristic picture of haemorrhagic infarction of the area involved, and also causing the clear clinical signs and symptoms—sudden, sharp pain in the chest, increase in the pulse rate, elevation of the temperature, cough, dyspnoea, haemoptysis, friction rub, râles, local impairment of the percussion note with change in the breath sounds, and more rarely cyanosis and shock. By embolism we mean the occlusion of the main trunk of the pulmonary artery or its principal branches by one or more emboli, giving rise to the grave picture so well known. Through our work we shall attempt to keep these two groups of cases distinct.

We present here the records of 51 different patients who had pulmonary infarction, pulmonary embolism, or both conditions. In these 51 cases, there were 34 instances of pulmonary infarction and 21 of pulmonary embolism. Of the 34 cases of infarction, five of the patients died; of the 21 cases of embolism, 19 patients died. We shall consider first the cases of pulmonary infarction, and then of pulmonary embolism.

#### PULMONARY INFARCTION

**Pathology.**—Post-operative haemorrhagic infarction of the lung occurs most frequently in the right lower lobe. This has been noted by many observers and agrees with our findings. The primary seat of the thrombus is usually in the peripheral veins, or the pelvis. The infarct is cone-shaped, with the base out, producing a raised surface upon the visceral pleura, the apex of the cone pointing toward the hilum of the lung. The pleura in the earliest stage is still smooth and

glistening, but soon becomes covered by a fibrinous deposit which gives rise to the friction rub heard in a majority of cases.

On section an infarct is solid, dark purplish-red in color, and generally presents a friable surface. The edges of an infarct are usually sharp and generally surrounded by an injected, inflammatory border. An old infarct may show signs of softening; in this case it is often gray in color.

Microscopically, the alveolar spaces are filled with red blood-cells, a few leucocytes, and are quite airless. The vessels leading to an area of infarction are found plugged by thrombotic emboli; the vessel walls may or may not show endarteritic changes.

Necrosis and cicatrization are rare. Absorption and re-establishment of the circulation usually take place through the pulmonary circulation in two or three weeks. With regard to this point, there is some difference of opinion, early observers claiming that resolution takes place through the bronchial system. When the infarction is due to infected emboli, abscess formation or gangrene may result. In one of our cases, a fatal pulmonary haemorrhage occurred in one of these abscesses.

As a result of a series of careful experiments on pulmonary embolism and infarction, Karsner<sup>18</sup> and his collaborators make the following observation:

The same laws for mixture of the blood of the bronchial and pulmonary vessels, laid down in connection with the circulation in the lung in general, apply also to the circulation in an area of embolism, i.e., there is no notable mixture of the bloods until the pressure in the one system or the other sinks to zero. Simple embolism of the pulmonary artery results in lower pressure in the embolic area, the pressure, however, not sinking to zero unless the blood supply of an entire lobe is cut off.

With normal pressures in the two vascular systems an area of pulmonary embolism involving less than the entire lobe receives its blood supply almost entirely from the rich anastomosis of the pulmonary artery between its own branches, and only when the bronchial pressure is raised to an extremely high point does the blood from this vessel play a notable part in the circulation in the area.

Zahn<sup>19</sup> demonstrated that passive congestion of the lung increased the likelihood of pulmonary infarction. This observation is in agreement with the work of Karsner, who reproduced this condition by tying the pulmonary vein or by compressing the lung by the introduction of sterile oil into the pleural cavity. In his experimental cases, Karsner found definite changes in the lung suggestive of infarction within three hours after the time of infarction and in 48 hours the pathological picture was complete. This is in accord with clinical observations. In practically all of our cases, no positive signs could be made out on the day of onset, while most cases showed a definite friction rub on the second day. According to Karsner's work, moreover, it required two or three weeks for the lung tissue to begin to function again after infarction.

These cases of sudden death which are produced by large "rider emboli" that obstruct both pulmonary arteries rarely show any pathological change in the lungs other than con-

gestion or œdema, unless the patient has had a previous infarction. This is illustrated by our autopsy cases.

*The Clinical Picture of Pulmonary Infarction.*—The first point we should like to present is the striking similarity between the clinical picture of the cases of pulmonary infarction and femoral thrombo-phlebitis, in regard to temperature and conditions of incidence.

With remarkable regularity, both conditions are found in the same type of patient and following the same type of operation. As regards age, infarction usually occurs before old age, only 1 case in 34 occurring above the age of 50 and 66 per cent of the cases between the ages of 20 and 40. Thrombosis shows the same age curve. Post-operative bronchitis and bronchopneumonia, on the other hand, are usually found in older patients.

As to the pre-operative condition, in 82 per cent it was good, in 18 per cent the patients were either anæmic, had a haemoglobin of 65 per cent or less, or for some reason were not in first-class condition. Practically all, however, came under the group of good surgical risks. In 26 per cent some elevation of temperature was noted before operation; considering the fact that 18 per cent were operated upon for some inflammatory condition, this is quite to be expected.

Of these cases of infarction 48 per cent followed operations for myoma, 18 per cent salpingitis, 9 per cent retroposition of the uterus, 8 per cent carcinoma of the uterus, 6 per cent carcinoma of the rectum and haemorrhoids; the remainder were equally divided between ovarian cysts, herniaæ, appendicitis and kidney conditions. The operations performed were: Abdominal hysterectomies, 45 per cent; abdominal panhysterectomies, 6 per cent; vaginal panhysterectomies, 3 per cent; myomectomies, 6 per cent; operations on the adnexa, 12 per cent; suspensions of the uterus, 9 per cent; appendectomies, 6 per cent; the remainder followed kidney and rectal operations and herniotomies. These averages show a rather close correspondence with those of thrombosis, with the exception that we have had no cases of infarction following perineal operations. Clark goes farther than this in saying that thrombosis never occurs after perineal work. We have found that 8 per cent of our cases of thrombosis occurred after this type of operation, and have had cases of fatal pulmonary embolism after the same procedures. We should, therefore, be surprised if we do not either see or hear of cases of infarction associated with perineal operations.

With regard to the time of appearance of infarction, the same relation to thrombosis is evident; in 75 per cent it occurred during the second and third weeks, in 20 per cent after the third week, in 5 per cent during the first week, and none came on before the fourth day. Post-operative bronchopneumonia and bronchitis usually follow the operation immediately.

The convalescence before the onset of infarction was febrile in almost all the cases, the temperature varying consistently between 99° and 100° F. In only one case out of 34 was the temperature curve normal before the day of infarction. It

is interesting that among the patients with infarction that showed no clinical evidence of phlebitis or femoral thrombosis, there was not a single case that had a clearly afebrile convalescence before infarction.\*

Complications such as infected wounds and other conditions that might cause a post-operative elevation of temperature have been eliminated; hence we feel that this picture is fairly constant. Petré has made this same observation with regard to embolism. Moreover, we believe it is what one might expect. In the type of case we are now considering, an infarction presupposes a thrombosis. Irrespective of the possible cause of thrombosis, we have found that a low febrile course precedes its manifestations in practically all instances; and that without exception in 205 cases there was a distinct elevation after the thrombosis became clinically evident. We feel, therefore, that the low protracted febrile course that precedes the infarction is due to the presence of a thrombosis.

After the infarction itself has actually occurred, the temperature curve shows a decided rise. As the clinical course of an infarction is usually short, in most cases a week suffices to see the temperature drop to its old level and most of the symptoms disappear. In a few cases the infarct is infected, and lung abscess or gangrene develops, usually with fatal results. In other cases, after the pulmonary signs and symptoms have cleared up, the temperature remains persistently between 99° and 100° F., or at times higher for two or three weeks. This temperature may be due either to the absorption of the infarct or to the thrombosis. The clinical significance of this type of temperature will be discussed later.

The interesting phase of the temperature curve is noted in the first few days. On the day of infarction the temperature is usually between 99° and 100° F.; in other words, it is not much higher than it has been continuously during the week or ten days before the infarction. It does not rise significantly until 24 hours after the infarction has occurred. We have noticed this in all but 2 out of 34 cases. Once elevated, the temperature curve is almost always of the hectic type, dropping in the morning and rising in the afternoon and evening. In these respects, infarction differs radically from the post-operative pneumonias, in which we have found that the temperature is distinctly elevated before the patient has any severe symptoms, rises progressively higher and is maintained at a high level. The second, third and fourth days of the infarction are usually the days of the highest fever, the temperature usually reaching 101°, at times 103° F. or more. The pulse usually accompanies the temperature, but the pulse curve seldom runs much above the temperature curve in ordinary cases.

*The Signs and Symptoms of Infarction.*—The symptoms that we have found in this series are striking. Pain on breathing is the outstanding feature. It has been present in every

\* Since writing this article, we have had the opportunity of observing three cases of uncomplicated post-operative pulmonary infarction. In these instances the general picture of pulmonary infarction which we describe in this article was strikingly developed, in regard to both the temperature curve and the clinical course of the disease.

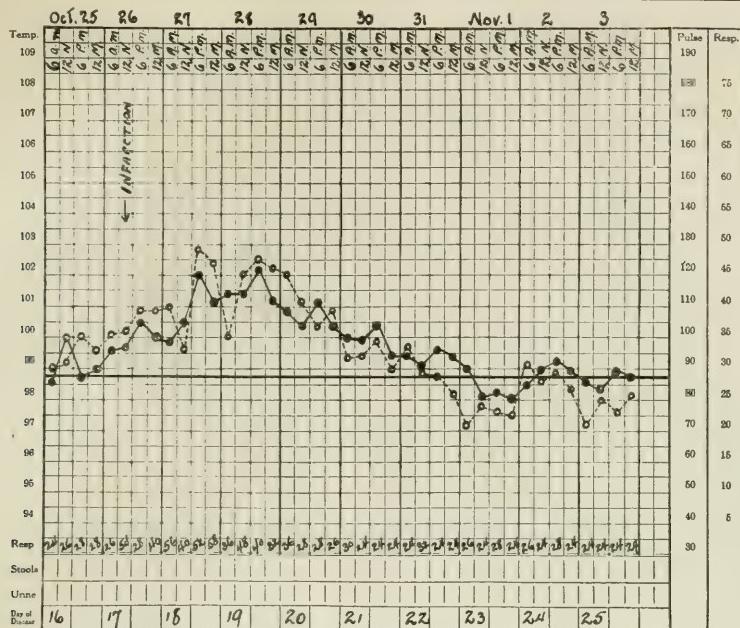


FIG. 3.—Temperature curve. Pulmonary infarction developing on seventeenth day after operation. Gynæcological No. 13296. The dots and solid lines indicate temperature. The rings and dashes indicate the pulse.

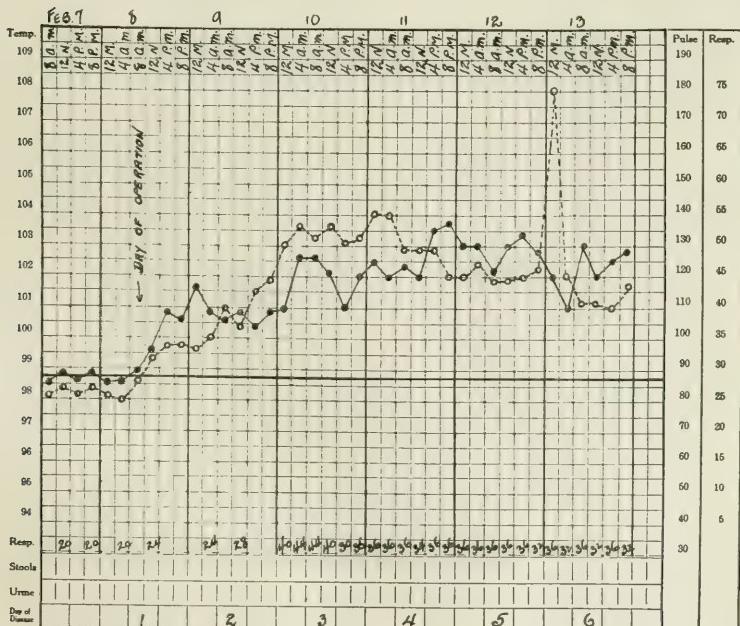


FIG. 4.—Temperature curve. Post-operative pneumonia, Gynæcological No. 17298. The dots and solid lines indicate the temperature; rings and dashed lines indicate the pulse.

one of our cases and has been the chief complaint. It is sudden in onset, usually very severe, making the taking of a deep breath almost impossible, requiring morphin frequently and in large doses. This pain is localized usually along the costal margin or over the lower ribs, usually in the axilla or below the scapula. In our cases, it was present on the right side four times as frequently as on the left. Both sides were simultaneously involved in two cases of this series. Pain is easily the first symptom in regard to time, prominence and regularity of appearance.

Compared with pain, cough is a rather minor symptom. One has to hunt through the histories to find the notes as to its presence. While we have found it in 63 per cent of our cases, when present it is usually not prominent, distressing or very productive. In this respect again, infarction differs from all types of post-operative inflammatory pulmonary complications.

Shortness of breath was present in 54 per cent of this series. It is usually not of the gasping, air-hunger type found in pulmonary embolism or severe secondary anaemia. The increased respiratory rate seems to be due chiefly to the inability of the patient to take a full deep inspiration without pain and the consequent substitution of a number of shallow respiratory movements. This symptom occurs on the day of infarction along with the pain.

Hæmoptysis we have found to be present in 36 per cent of our cases. If hæmoptysis be the *sine qua non* in the diagnosis of post-operative pulmonary infarction, as many text-books teach, we are afraid that two-thirds of the cases will be missed. Collapse and cyanosis are not frequent in infarction, unless the condition of the patient is extremely poor, or the infarction rather grave.

Anxiety and fear of impending death are not infrequently seen. The suddenness of the attack, the piercing thoracic pain and dyspnoea accompanied at times by sweats or chills, cannot but fail occasionally to produce a mental perturbation in a patient just recovering from a surgical operation.

Of the physical signs, the presence of the friction rub is the most characteristic. It has been noted in 75 per cent of our cases. Râles have been found in the same number, impairment of the percussion note and changes in the breath sounds in 63 per cent.

In the classical case of pulmonary infarction, the presence of all the characteristic symptoms and physical signs should make the diagnosis fairly certain. Unfortunately, however, these sign-posts are not always present. It is in such atypical instances as this, where there may be no friction rub or no hæmoptysis, that the clinical associations of pulmonary infarction come to our rescue and act as our guide. And these associated conditions, together with the immediate signs and symptoms, go to complete the clinical picture of pulmonary infarction.

We have already called attention to various factors in the clinical picture of infarction; its relation to the type of operation; the low febrile prodromal convalescence; the time of occurrence; its immediate clinical manifestations; and its usual

course. The elements in the clinical picture which we would now present are: (1) Its association with femoral thrombophlebitis; (2) its association with repeated infarction; and (3) its association with pulmonary embolism.

*Pulmonary Infarction and Femoral Thrombophlebitis.*—We have noticed that pulmonary infarction and femoral thrombophlebitis are associated causally. They occur in the same type of patient, in the same age period, following the same groups of operations, in the same period of post-operative convalescence, and are preceded by the same low, continuous prodromal temperature. Our series shows, moreover, that the relation between thrombosis and infarction is closer even than this, for we have repeatedly found both complications in the same patient. In 41 per cent of our cases of pulmonary infarction there was venous thrombosis, with pain and swelling of the leg. In this group showing both conditions, the leg symptoms appeared before the pulmonary in 57 per cent of the cases. In 43 per cent the patients developed the infarction first, and a few days later pain and swelling of the leg appeared. We consider this clinical association to be strong confirmatory evidence in the diagnosis of pulmonary infarction.

*Repeated Attacks of Pulmonary Infarction.*—Although repeated attacks of pulmonary infarction in the same patient are not of every-day occurrence, they are not rare. In 10 per cent of our cases, the first infarction was followed by a second. We have no record of three distinct attacks of pulmonary infarction in the same patient. The time interval between attacks varied from 10 days to two weeks. In two-thirds of our cases, the second attack was more severe than the first. This is what one might expect, however, for in the short interval of 10 days, it is probable that in accordance with the recent experimental work of Karsner and Ash,<sup>20</sup> the lung tissue consolidated by the former infarction had not yet returned to normal function, and the subsequent sudden elimination of still another portion of the pulmonary reserve would naturally be accomplished by still greater reaction on the part of the patient. This is shown rather clearly by one case in which the second attack was all but fatal, although the physical signs that developed later seemed to indicate that the second infarction was limited entirely to the left lower lobe and apparently involved only a part of it.

*Infarction and Embolism.*—Infarction may be associated also with subsequent embolism. In this series of cases, embolism has occurred after infarction rather more frequently than a repetition of the infarction itself. In 12 per cent of our cases of infarction pulmonary embolism developed later, half of these cases of embolism being fatal. The time interval between the infarction and embolism varied from 10 days to three weeks.

In studying the records of the convalescence of these patients that had second attacks of either infarction or embolism superimposed upon an earlier attack, we noticed that the temperature had not fallen to normal in any case before the second supervened, even though there might have been an interval of three weeks between attacks. This is not the usual course of a case of pulmonary infarction. In a typical instance, the tempera-

ture commences to drop on the fourth or fifth day after infarction; in 10 days it is either normal or very nearly so and the symptoms have entirely cleared up. Careful examination of the chest may show a residuum of only a few physical signs.

An elevation of temperature persisting for over a period of two weeks following an infarction usually means a complication. Our commonest complications have been lung abscess, bronchopneumonia, pulmonary gangrene, miliary abscesses and septicæmia. All of these usually give definite symptoms which immediately offer a clue in discovering the cause of the fever. But excluding cases with these complications, all of our cases of repeated infarction or embolism showed between the attacks a definite persistent pyrexia, seldom exceeding 100° F. During this interval these patients have absolutely no discomfort, no localizing signs and no symptoms explanatory of the elevation. We believe that the association of this unexplained elevation of temperature with cases of repeated infarction and embolism indicates that the same conditions which gave rise to the primary infarction are still present and active, and under certain circumstances might lead to the same results again.

The relation of the temperature to thrombosis and embolism has been emphasized before. Two foreign observers have confirmed our findings in this respect. In 1912 Michaelis<sup>13</sup> stated that "post-operative and post-partum thrombosis and embolism do not occur wholly without premonitory signs; if the temperature is taken frequently and accurately enough, one will observe a low febrile temperature before the onset of these complications. In a patient that does not have this low elevation, we do not need to fear the possible development of thrombosis or embolism." Petréen supports Michaelis in his clinical observations, but does not indulge in prophecy.

On the basis of our series of cases, we believe we can make the same application to infarction and particularly to cases of repeated infarction or embolism. Although we would not go so far as to say that patients who have a perfectly normal temperature during convalescence will not develop thrombosis, infarction or embolism, yet we feel that the presence of a persistent, low, unexplained fever late in convalescence should make one think of these complications. By way of illustration, we might cite as a rather typical case, a patient who on the 12th day had a mild attack of post-operative infarction which was diagnosed as pleurisy. In a week her symptoms had cleared up completely, and at the end of two weeks, the physical signs in the chest were negative. She still had an elevation of temperature reaching 100° or 101° F. every night, with no localizing signs or symptoms. Her sputum was examined for tubercle bacilli, her operative wound had healed, she had no pain or swelling of the leg, and no cause for the elevation was found. As she was feeling perfectly well, she began to chafe under confinement in bed, and demanded that she should be allowed to go home. On the 21st day after her infarction, she was therefore discharged from the hospital, and while walking around the ward telling the patients goodbye, had a fatal attack of pulmonary embolism, dying almost instantaneously.

These cases emphasize two points: (1) The importance of diagnosing pulmonary infarction; and (2) the necessity of keeping patients who have had a pulmonary infarction in bed until their temperature is normal. We would not presume to state that pulmonary embolism can be avoided by keeping patients in bed, for our records show that many cases of embolism occur in the first week of convalescence; moreover, patients well along in convalescence have had an embolism during the night while merely turning over in bed. On the basis of these records, however, we feel certain that the presence of a low febrile temperature for two or three weeks following an infarction should be a distinct indication to keep that patient as quiet as possible until the temperature is normal, or until a definite cause for the elevation has been established.

*Causes of Death in Pulmonary Infarction.*—Pulmonary infarction in itself usually runs a short course and the patient recovers. Because of its occasional association with serious complications, however, it may take a more grave aspect.

These complications are due to: (1) Septic emboli, which give rise to infected infarctions; (2) bland infarctions in a lung already infected; and (3) second attacks of either pulmonary infarction or embolism.

Of our 34 cases of infarction, in five the patients died, a mortality of about 15 per cent. The causes of death in these cases were:

Gangrene of the lung .....	2 cases.
Abscess of the lung, uncomplicated .....	1 case.
Abscess of the lung with terminal pulmonary embolism..	1 case.
Pulmonary embolism, uncomplicated .....	1 case.

All but one of these five cases came to autopsy. The only one that was not examined post mortem was a case in which death had occurred from a typical pulmonary embolism three weeks after the day of infarction. The terminal event of one of the cases of gangrene was an intrapulmonary haemorrhage, due to the necrotic perforations of the vessels in the gangrenous lobe. Lung abscesses due to septic emboli are often associated with septicæmia and metastatic abscesses in the liver, spleen and kidneys. At the close of the article we shall include detailed reports of cases representing each of the above types of infarction.

As a rule, attacks of infarction occurring during the first week of convalescence are apt to be more serious than those that develop later. During the first few days after an operation, the general resistance of a patient is low and a small embolus might produce a degree of shock out of all proportion to its size. Then again, for several days after an ether anaesthetic, the lungs may be irritated, slightly congested and there may be a mild bronchitis. An infarct in such a lung might furnish an ideal culture medium in which a low grade infection might develop into full virulence. It is noteworthy that in this series of cases, in half of the patients that died of pulmonary abscess or gangrene the infarctions had appeared definitely before the sixth day after operation. In the remaining patients that died of these complications, it was impossible to fix the exact date of infarction.

*The Treatment of Pulmonary Infarction.*—The treatment of pulmonary infarction is symptomatic and expectant; symptomatic in that nothing radical can be done to cure the infarction; expectant in watching the developments of the case and attempting to prevent further complications.

The symptoms which require therapeutic attention are pain, dyspnea, cyanosis, shock, anxiety and restlessness. Cyanosis and shock are rarely present, and the cough is not often distressing. For the pain, morphin is strongly indicated. We see no reason why it should not be given in sufficiently large dosage to keep the patient as quiet as possible. Strapping of the chest by broad strips of adhesive may relieve the pain by mechanically lessening the pleural movements on the side affected.

Dyspnoea is usually present, often in ratio to the severity of the pain. The relief of the pain will lessen the dyspnoea. Fowler's position may make the respirations easier. When the dyspnoea is accompanied by cyanosis, it usually means real insufficient oxidation of the blood, and requires active therapy. In this type of case, oxygen may give instant relief not only in clearing up the cyanosis, but also in lessening the respiratory rate. This in turn relieves the patient of exhaustion, rests the heart, lowers the pulse rate and calms the restlessness and anxiety of the patient. Fresh air is also of value for the same reason. Of drugs, we have combined atropin with morphin, especially in the presence of a productive cough; strychnin, strophanthin and caffein are also useful. It is not often, however, that a case of infarction requires such active stimulation.

The anxiety and restlessness of the patient may be out of all proportion to the severity of the lesion. These must be controlled, as the danger of secondary infarction or embolism is always present. Rest is essential, and for this purpose the treatment we have outlined above is our chief reliance. In addition to this, firm assurance and encouragement may play no small part in helping the patient over the critical period of her convalescence.

After the first 48 hours, the acute symptoms usually disappear and we pursue a course of expectancy. If the temperature falls to normal after 10 days or two weeks, we feel assured that the greatest danger is past and that the infarct is resolving normally without complications. If, however, pulmonary symptoms continue, the temperature mounts steadily higher and the physical signs accumulate rather than disappear, we probably have to deal with an infected infarct and this is usually a serious matter. In our series, this happened in 10 per cent of the cases.

Usually, however, the infarction pursues its short course, the pulmonary symptoms clear up in about a week, the signs may linger a week or 10 days longer and with their disappearance the temperature reaches normal. After this event, we tentatively let the patient up in a chair. If no accident follows, we allow her to walk, and in a day or so she goes home. As we have stated before, we can in no way indorse the practice of letting patients out of bed following pulmonary infarction

until the temperature is distinctly normal. This is a hard rule to enforce, as patients, who have no symptoms and feel perfectly well, chafe under prolonged confinement. It is, nevertheless, the only safe rule to follow.

*The Recognition of Pulmonary Infarction in Clinics Other Than Our Own.*—It is needless to say that we were surprised when we observed the almost regular consistency with which the diagnosis of pulmonary infarction has been missed in our own clinic. Only 10 per cent of our cases have been recognized. We, therefore, examined the literature, the recent textbooks and the reports of other large clinics to see whether this complication was being recognized elsewhere, for "Misery likes company."

The literature on post-operative thrombosis and embolism practically always mentions infarction as a possibility. This is particularly true of the foreign articles. In the case reports of post-operative pulmonary complications, however, there seems to be a marked silence with regard to the subject. Standard text-books seem to ignore it. One large volume published recently, in devoting almost a thousand pages to surgical after-treatment, does not mention it. Infarction is not even found in the index. In 1913 and 1917, respectively, rather extensive articles appeared in the medical literature, reporting, in detail with case histories, the post-operative pulmonary complications in two of the largest and most up-to-date surgical clinics in America. Extensive bacteriological studies in the various types of post-operative pneumonias were reported, but not a single case of pulmonary infarction is mentioned. It is true that the author of one of these articles made the statement that small emboli might possibly be the cause of some post-operative pulmonary complications, but in not one instance is the diagnosis of pulmonary infarction made. All these cases were diagnosed either as pneumonia, bronchopneumonia or pleurisy. In looking over these reports in detail, we feel certain that some of the cases were undoubtedly pulmonary infarctions and should have been so diagnosed. Furthermore, if the reports of these two large clinics, together with our own, show such records as this, it is highly probable that the profession at large is no more wide awake to the true nature of the complication.

*The Diagnosis of Pulmonary Infarction.*—In our clinic the diagnosis of pulmonary infarction has been anything but good. We have recognized only 10 per cent of our cases. What is the explanation of such a poor record? The answer is simple—the diagnosis had been based practically always upon the physical findings in the thorax instead of the whole clinical picture.

Let us consider, then, the different items that constitute the clinical picture in one of these cases.

*Class of Case:* To begin with, we are dealing with a post-operative patient who is convalescing from a laparotomy, frequently a hysterectomy.

*Time of Occurrence:* This complication occurs practically always in the second or third week after operation.

*Temperature:* The temperature curve is quite characteristic when not complicated by other factors. The patient has a low unexplained evening temperature of 99° to 100° F. after operation. After the day of the infarction, the temperature rises sharply, but seldom goes much above 102° F. The curve is hectic in type, not like that of pneumonia. It reaches its highest point between the second and fourth days and usually drops almost to normal again at the end of a week.

*Attack:* Infarction almost always makes its appearance in an acute attack with sharp sticking pain over the ribs as the dominant symptom. The attack may be accompanied by a definite chill; this, however, is rare. Chilly sensations are not infrequent.

*Leucocyte Count:* This usually varies between 12,000 and 18,000, and is of little help in the diagnosis.

*Physical Signs:* The physical signs rarely make their appearance before the second day. The most constant of these is the friction rub, which was noted in 75 per cent of our cases. It probably is present in a greater number, but this represents only those cases in which it was noted upon the history. Râles were heard in 75 per cent of our cases; they are usually evident a little later than the friction rub. Impairment and changes in the breath sounds appear last and were noted in 63 per cent of our cases.

*Symptoms:* Pain ushers in the attack and is always the predominant symptom. Cough, while present in 63 per cent of our cases at some time, is usually not severe, and in most cases is unproductive. Haemoptysis was present in 36 per cent of our cases and when present, practically clinches the diagnosis. Phlebitis, pain and swelling of the leg occurred in 41 per cent of this series, and when present is just as confirmatory as haemoptysis.

*A Typical Case of Pulmonary Infarction.*—It might be of interest to describe a typical case of pulmonary infarction. Let us take a well-nourished woman 40 years of age, who has had a hysterectomy for a myomatous uterus. She is returned to the ward in good condition, has a slight post-operative reaction and then settles down to a satisfactory convalescence. The wound is dressed by the ward surgeon, found to be clean and the stitches are removed. On account of a slight daily rise of temperature to 99.5° F., he examines the wound very closely for stitch infection. The patient continues to improve, has no discomfort, and is allowed to be up on the 14th day. Suddenly she is seized with sharp pain in her right side, more especially on deep inspiration. The nurse promptly returns her to bed and takes her temperature, finding it to be 100° F. The ward doctor is informed, makes a careful examination of the chest, but finds nothing definite. The patient is reassured and forgotten. On the following morning, in making his rounds, the doctor is informed that his patient still complains of pain in her right side and that her temperature is 102° F. He goes over the chest promptly, finds a friction rub, with a few râles below the angle of the scapula and makes a diagnosis of dry pleurisy. A day or two later the patient may develop haemoptysis or phlebitis of the leg. She usually makes a

prompt recovery and in 10 days the little pulmonary upset is a thing of the past and forgotten.

*Differential Diagnosis.*—The conditions from which pulmonary infarction must be differentiated, named in the order of their frequency, are: Pleurisy, pneumonia, pulmonary tuberculosis, bronchitis, empyema, gangrene of the lung, pulmonary abscess and subdiaphragmatic abscess.

Of the cases diagnosed as post-operative pleurisy in this clinic, we believe that 45 per cent were infarctions. Of course, we realize that these patients did have a fibrinous pleurisy so that in a way the diagnosis was correct. The important fact, however, that the pleurisy depended upon an infarct, was overlooked. A dry fibrinous pleurisy of other origin would be hard to differentiate and the diagnosis would depend upon the later development of consolidation or haemoptysis. Sero-fibrinous pleurisy should be easily differentiated by the presence of the pleural effusion and exploratory puncture with the needle. A previous history of tuberculosis would be helpful. Many cases of criminal abortions and severe puerperal infection develop pleurisy, generally associated, however, with peritonitis, pneumonia or metastatic lung abscesses.

Pneumonia might offer difficulties in the early stages, but when the clinical picture is complete, it should be readily differentiated. Of our cases 12.5 per cent diagnosed as post-operative pneumonia were due to pulmonary infarctions. The onset of pneumonia is usually immediately after the operation, the temperature rises quickly and is sustained. Cyanosis is more marked, the leucocyte count higher and the sputum usually rusty instead of bright red. The course of pneumonia is more severe than that of a simple infarction, and the patient is distinctly more toxic.

An old latent tuberculosis lesion in the lung is not an infrequent cause of trouble in operative cases. These patients may show a reactivation of their old process; it usually takes place very soon after operation; the temperature curve may be very irregular; there is generally a profuse muco-purulent expectoration against little or no expectoration in infarction. The presence of haemoptysis in infarction almost always makes one think of tuberculosis, and in many of our cases tubercle bacilli were repeatedly searched for. The finding of the tubercle bacilli, the location of the apical pulmonary lesion, the history and X-ray should aid in clearing up the diagnosis.

In our cases bronchitis apparently offered no confusion in diagnosis, for none of our infarctions were mistaken for this condition. The absence of pain and friction rub, the presence of a profuse expectoration with a distressing cough, the onset immediately after operation, the low temperature and different physical signs, usually separate these cases clearly.

Empyema, lung abscess and gangrene of the lung occasionally develop in infected infarcts. The onset of infarction should serve to show the true nature of the complication. Empyema, however, more often follows pneumonia and should not be confused with a simple infarct. Post-operative gangrene of the lung may also follow pneumonia or the

aspiration of foreign material. The history, sputum and X-ray should clear up the diagnosis. Subdiaphragmatic abscess should be differentiated on the basis of abdominal symptoms and the X-ray. These patients are also usually more toxic than those suffering from infarction.

What right have we to make a diagnosis of pulmonary infarction upon the basis of the clinical records without even having seen these patients? We feel that it cannot be done in all cases, and consequently have rejected many cases in which the data seemed to be insufficient. The diagnosis, we repeat, must be based upon the complete clinical picture and not upon the physical findings alone.

Let us subject our 34 cases of infarction to a brief analysis. Out of these 34 cases, in only 12 was there neither haemoptysis nor phlebitis. We assume these conditions to be very strong confirmatory evidence where a clinical picture of infarction exists. Of these 12 patients five died; in four of these autopsy proved the presence of the infarct, the fifth died of typical pulmonary embolism. Of the remaining seven, one had two typical attacks separated by an interval of one week. In the remaining six cases we were not aided by the presence of haemoptysis or phlebitis, but based our diagnosis upon the history of typical attacks occurring between the 9th and 18th days with the usual physical findings and characteristic temperature curve.

#### POST-OPERATIVE PULMONARY EMBOLISM

We shall now conclude by mentioning the cases of pulmonary embolism we have encountered. There is such a wide literature on this subject that we shall attempt to bring out only two points: (1) The relation of pulmonary embolism to pulmonary infarction and thrombophlebitis; and (2) unusual symptoms that may be found in pulmonary embolism.

We have had 21 cases of pulmonary embolism in this series. As we have stated before, we separated them from the cases of infarction because both pathologically and clinically they offer certain marked points of difference, though at basis they have the same etiology.

*The Pathology of Embolism.*—Of 19 cases of fatal pulmonary embolism, all but two came to autopsy. These two patients died in attacks that were clinically absolutely typical.

From the pathological viewpoint, there is very little similarity in the appearance of a lung the site of a pulmonary infarct and a pulmonary embolus. The lungs of a patient dead of sudden pulmonary embolism rarely show any lesion beyond oedema and congestion. We have never observed the picture of haemorrhagic infarction in any of these cases unless the patient has had an infarct before the fatal embolism occurred. Occasionally there has been a moderate hydrothorax and a slight increase in the quantity of pericardial fluid. Dilatation of the right heart and of the superior and inferior vena cava is usually marked.

In case a patient lives several hours after embolism, patches of bronchopneumonia may be found in addition to the oedema.

We have found the usual source of pulmonary emboli to be the pelvic veins; in 15 per cent of our cases the origin was in the veins of the leg.

There is a border-line group of cases that we have not had the opportunity of studying pathologically. We refer to the cases in which there were large emboli, but of insufficient size to cause death. At the onset of the attack these cases present the typical clinical picture of grave pulmonary embolism. Within two or three days, however, the signs of infarction come to the fore.

We have had two such cases and from them have been able to gather a rather interesting symptomatology. Pain is almost not felt in these attacks. Although death from pulmonary embolism is always tragic, it is probably almost painless. The chief complaint of these patients has been a feeling of immense weight in the substernal region of the chest, which seemed to make it impossible for them to breathe. While the point has almost no clinical value, it is to be noted that most patients showing this symptom die.

*The Occurrence of Pulmonary Embolism.*—Although pulmonary embolism may follow almost any type of surgical procedure, it is usually associated with laparotomies. One of our cases occurred during the convalescence after closure of a vesico-vaginal fistula.

Pulmonary embolism may occur at any time during convalescence. It is apt to happen earlier than either pulmonary infarction or thrombophlebitis. One of our patients had a fatal attack three hours after operation, another at the end of 24 hours. Half of our cases developed within the first six days; practically all of the rest of them during the second week.

Pulmonary embolism is much more serious, of course, than pulmonary infarction. Fifteen per cent of our cases of infarction died; 90 per cent of our cases of embolism. Both groups of cases almost uniformly show a low febrile convalescence up until the day of infarction or embolism. In 80 per cent of our cases of embolism there had been a daily unexplained rise in temperature, reaching at least 99.4° F. until the day of embolism. In some cases the temperature had been as high as 101° F. every day for a period of 10 days or more before the attack.

We have seen that a patient may have repeated attacks of pulmonary infarction and that the second is usually more serious than the first. Repeated attacks of pulmonary embolism are not so common, principally because the first is almost always fatal. Three of our patients apparently died during second attacks of pulmonary embolism, the second attack being superimposed upon the first after an interval of from 1 to 15 hours. No patient survived the second attack of embolism.

*Pulmonary Embolism and Thrombophlebitis.*—The relation between thrombophlebitis and pulmonary embolism is not as clear as it might be. It seems to be an established fact that pulmonary embolism does not often occur in patients who have pain and swelling of the leg. Out of a group of 205

patients who showed clinical signs of thrombophlebitis, we have had only three cases of pulmonary embolism. On the other hand, in this same group there were 14 instances of pulmonary infarction. In only 10 per cent of our cases of pulmonary embolism were there pain and swelling of the leg, whereas in almost half of our cases of infarction they were present.

The infrequency with which pulmonary embolism is associated with pain and swelling of the leg is brought out more strikingly yet by this series. Out of 21 cases of pulmonary embolism in only three had there been a thrombophlebitis, and two of these three patients are the only ones that suffered from pulmonary embolism that did not prove fatal. In other words, we have had only one single fatal case of pulmonary embolism in 205 consecutive cases of thrombophlebitis. These represent all the cases of thrombophlebitis following 21,000 gynaecological operations—a rather remarkable record.

Why these two conditions are not more frequently associated is rather difficult to explain. We have heard of very little experimental work having been done to clarify this situation. Reasoning from a purely clinical basis, however, it seems to us that the explanation for this phenomenon is apt to be found in the nature of the thrombophlebitis with which we are dealing. If traumatism and infection are the chief causes of thrombosis, femoral thrombosis associated with pain and swelling seems to us to show the characteristics of an inflammatory process. All the cardinal signs of local inflammation are present in a typical case of this sort. There is pain along the course of the femoral vessel and also in the leg; swelling is present, local tenderness is usually noted; the surface temperature is often elevated; even redness of the skin in the region immediately surrounding the thrombus may be present. Whether, as a result of this evident inflammatory reaction, the thrombus becomes so adherent to the vessel wall that it cannot often be dislodged, is a mere supposition of ours that needs further confirmation.

On the other hand, it seems probable that traumatic and mechanical factors play a larger part in the formation of pelvic than in this type of femoral thrombosis. The inflammatory picture is not striking in the cases of pelvic thrombosis with embolism, as it is in femoral thrombosis with pain and swelling of the leg.

It is rather difficult to carry this analogy from the femoral vein to the veins of the pelvis, for the anatomical situation of the iliac and the ovarian plexus makes the symptomatology associated with their thrombosis somewhat obscure. For this reason the diagnosis of pelvic thrombosis is almost never made clinically; it is usually recognized only on the operating table or at autopsy. Consequently, it would be very difficult to make a clinical differentiation between inflammatory and traumatic types of pelvic thrombosis in their relation to pulmonary embolism.

There are, nevertheless, certain clinical facts which lead us to believe that traumatic thrombosis of the pelvis veins is more often associated with embolism than the inflammatory type. Autopsy records show that in 85 per cent of our cases

of fatal pulmonary embolism the origin of the embolus was in the pelvic veins. In these cases, the thrombosis was symptomless. It caused no discomfort whatever. This is in rather sharp contrast with the severe pain associated with femoral thrombosis. In the second place, pelvic thrombosis associated with embolism is apt to occur earlier in convalescence than femoral thrombosis with pain and swelling of the leg. Half of our cases of embolism occurred during the first week of convalescence, two within 24 hours after the operation. Femoral thrombosis almost never occurs as early as this. This may indicate a different etiology. In the third place, thrombosis of the pelvic veins in severe pelvic inflammatory disease without operation almost never gives rise to embolism. In these cases of thrombosis there has been no operative trauma and it seems that the thrombosis must be purely infectious in origin. This type of thrombosis is seen not infrequently on the operating table in the presence of very extensive and severe pelvic inflammatory disease, with cellulitis of the broad ligaments. In these cases one may at times cut across a broad vascular base with almost no bleeding, owing entirely to the inflammatory thrombosis of the vessels. Yet sudden death from pulmonary embolism occurring before operation is almost unheard of in connection with pelvic inflammatory disease. In the fourth place, the mechanical factors conducive toward thrombosis are very marked in the pelvic vessels. These veins are large, tortuous, are directly subjected to the trauma of the operation, are clamped and ligated. Autopsy shows, moreover, that in a considerable proportion of these cases, no gross evidence of infection can be found.

While the above evidence seems to point toward traumatic thrombosis as the usual cause of pulmonary embolism, we would not for a moment state that thrombosis with inflammatory signs cannot cause embolism. For in definite instances, as we have shown, clinical and pathological evidence points to quite the contrary view. This, moreover, is what one would expect. Infection and trauma are both involved in the etiology of venous thrombosis, and just so far as the clinical differentiation of these two types of thrombosis is not clear, to that extent we must admit that it is impossible to associate the occurrence of pulmonary embolism with either type in any definite causal relationship. Cultures from large amounts of centrifugalized blood taken from patients exhibiting symptoms of phlebitis and infarction might show an increasing number to be associated with infection. The solution of this question might possibly lie in the routine microscopic and bacteriological examinations of the thrombus, the vessel wall and the surrounding tissues. Unfortunately, the records on this phase of the question are insufficient to make any valid deductions. Until some such co-ordinated study as this is done on the clinical and pathological aspects of the venous thrombosis and pulmonary embolism, we feel that the final explanation of these problems will remain in abeyance.

*The Diagnosis of Pulmonary Embolism.*—Pulmonary embolism is usually not difficult to recognize. This is especially true in the typical case in which death occurs very soon after

the onset of symptoms. As about 50 per cent of our patients died within 30 minutes, the diagnosis offered but little confusion. Pulmonary embolism, however, is neither always fatal nor even rapidly fatal. In 25 per cent of our cases the patients lived as long as an hour after the beginning of the attack, and in 15 per cent from 15 to 24 hours. In 10 per cent there was complete recovery.

The chief diagnostic interest centers about that group of cases in which death is deferred for some time after the onset of the attack. During this period of from 15 to 24 hours, the most varied and remarkable clinical pictures may develop. As a result of this, these cases have been mistaken for cerebral embolism, intracranial haemorrhage, epilepsy, hysteria, post-operative shock and intra-abdominal haemorrhage.

When we consider the type of lesion with which we are dealing, this confusion of symptoms leaves little cause for wonder. On the basis of the pathology of pulmonary embolism, almost any clinical picture can be explained. The sudden and more or less complete occlusion of the pulmonary artery to all intents and purposes immediately eliminates oxidation of the blood, mechanically cause a dilatation of the right heart and engorgement of the superior and inferior vena cava, acute congestion and stasis of the blood supply in the abdominal viscera, the brain and extremities. Such a complete vascular disorganization as this at once produces the most profound shock, asphyxiation of the tissues and a host of secondary disturbances of the entire nervous system. Furthermore, in patients who have developed thrombosis of the pelvic plexus or the femoral vein, there might also be a concomitant thrombosis in some unusual location, as we have seen in this series of cases. It is quite possible that in no small number of instances unusual symptoms might be due to the occlusion of a vessel which is not commonly the site of post-operative thrombosis; for example, in the portal or the cerebral circulation. These anatomical and physiological changes give rise to the grave picture of pulmonary embolism, its overwhelming collapse, dyspnoea, cyanosis, rapid, thready and irregular pulse, neurological and abdominal manifestations and usually a fatal termination.

Bearing in mind the variety of physiological disturbances that accompany pulmonary embolism, we may readily understand the various clinical manifestations it may take, provided the patient lives long enough to develop them. The atypical symptoms which we have observed most frequently fall into two groups: first, neurological; second, abdominal.

In the first group of cases, of which we have three, the localizing symptoms were chiefly cerebral. Crossed paralyses, spasticity or twitching of the muscles of one side of the face, irregularity of the pupils, ocular deviations, heavy and inarticulate speech, general epileptiform convulsions interspersed with intervals of deep coma have all been noted in these cases. Sometimes the pulse may become full and strong after the initial shock of the attack has passed away. As a terminal event, the temperature may rise rapidly to  $104^{\circ}$  or  $105^{\circ}\text{F}$ . In this type of pulmonary embolism, especially when associated with hypertension and advanced

age, the idea of intracranial haemorrhage or cerebral embolus might readily be entertained.

In another group of instances the abdominal symptoms predominate. We have seen two of this type. In cases of this character, abdominal pain, distension, tenderness, nausea, vomiting, a weak and thready pulse and cold extremities might readily lead one to think of intra-abdominal haemorrhage or post-operative obstruction. At the close of this paper will be found the detailed report of one case of this character that was seen by the chiefs of two departments and operated upon for intra-abdominal haemorrhage. The possibility of embolism was considered, but haemorrhagic shock seemed to be the prevailing view. Fortunately, this patient survived both the operation and embolism. Embolism may simulate post-operative shock, particularly when it occurs early in the convalescence and in a patient in poor condition.

All but one of these patients with atypical symptoms died, and autopsy revealed an uncomplicated pulmonary embolism. The only patient that lived was the one that was operated upon for intra-abdominal haemorrhage. This possibility was eliminated by the operation and the diagnosis of pulmonary embolus was made on the pulmonary picture which developed, the fact that two weeks before the embolism this patient had a typical pulmonary infarction which was diagnosed as pleurisy, and that two days after the second operation she developed femoral phlebitis.

These cases merely go to show that whatever aids can be brought to bear in the diagnosis of post-operative pulmonary complications clarify the view and place post-operative treatment on a more rational basis; after all, it is the clinical picture as a whole that counts, usually far more than any single physical finding. This paper has been virtually a post-mortem examination of the mistakes that have been common in the diagnosis of post-operative pulmonary conditions; and while post-mortems are at times embarrassing, they still have their advantages. In this article we have attempted to point out a few of the main clinical features of a group of post-operative pulmonary complications that have heretofore usually passed unrecognized. This we have done in the hope that, if recognized, these complications may be treated in a more satisfactory manner and, if possible, their more serious sequelæ avoided.

#### CONCLUSIONS

1. Post-operative venous phlebitis and thrombosis are not peculiar to any particular type of gynaecological operations.
2. There are a number of conditions that favor thrombus formation. Of these, we feel that infection and trauma play the most important part.
3. Perineal operations are not free from these complications.
4. Practically all cases of thrombophlebitis are associated with a slight rise in the temperature curve.
5. Phlebitis and thrombosis of the leg veins when associated with pain and swelling are rarely ever followed by fatal embolism.

6. Pulmonary infarction occurs most often in the same class of cases and during the same period of convalescence as femoral thrombophlebitis.

7. Pulmonary infarction may precede pulmonary embolism.

8. Post-operative pulmonary infarction in the majority of cases has heretofore been unrecognized.

9. The diagnosis of post-operative pulmonary infarction must be based on the clinical picture rather than the physical findings alone.

10. We believe that with proper care, pulmonary infarction should be diagnosed.

**Note.**—Since the completion of this paper our attention has been called by Dr. Howard A. Kelly to a short article on this subject published in 1902 by Dr. G. Brown Miller,<sup>23</sup> formerly resident gynaecologist of this hospital. After reviewing a series of 16 cases which had been diagnosed as post-operative pleurisy, he arrived at the conclusion that eight of them were primarily due to pulmonary infarction. Seven of these eight cases are included in our series; the eighth case, which Dr. Miller presented, we have not included, because we felt that the data were insufficient to make a diagnosis. Dr. Miller himself stated that he was not certain that this case was one of infarction.

That two groups of observers, separated by 17 years, should independently pick out the same cases from a large number of post-operative pulmonary complications and reach the same conclusions, is a rather unusual coincidence. Even though Dr. Miller presented but a small series of cases and did not have the opportunity to establish any of his impressions by autopsy confirmation, it must be stated that he presented a clean-cut clinical picture of pulmonary infarction and was probably one of the first to call attention to the frequency with which it is confused with pneumonia and pleurisy. We are in complete accord with many of the opinions which he advanced.

#### CASE REPORTS

1. Gyn. No. 8222. Fatal pulmonary embolism with previous infarction.

2. Gyn. No. 3492. Atypical pulmonary embolism with abdominal symptoms. Previous infarction. Embolism diagnosed intra-abdominal hemorrhage. Exploratory laparotomy. Femoral thrombosis following embolism. Recovery.

3. Gyn. No. 24894. Atypical pulmonary embolism with cerebral symptoms. Autopsy No. 5920.

4. Gyn. No. 13296. Typical case of bland pulmonary infarction. Recovery.

5. Gyn. No. 12587. Pulmonary infarction, multiple. Secondary lung abscesses. Death. Autopsy No. 2651.

6. Gyn. No. 17670. Pulmonary infarction. Gangrene of lungs, with terminal pulmonary hemorrhages. Death. Autopsy No. 3585.

**CASE 1.—Gyn. No. 8222. Fatal pulmonary embolism with previous infarction.**

Mrs. H., aged 27. One child.

**Complaint.**—Pain in epigastrium, with attack of indigestion.

**Diagnosis.**—Retroposition of uterus. Laceration of perineum.

**Operations.**—October 17, 1900. Suspension of uterus. Perineorrhaphy. Gall-bladder and pylorus negative.

**Post-Operative Notes.**—October 21, 1900. Condition of patient good. Has been having a slight elevation of temperature; perfectly comfortable.

October 23, 1900. Stitches removed. No pain in abdominal wound. No evidence of inflammation in pelvis. Wound in excellent condition. Temperature still slightly elevated.

October 28, 1900. For the last few days the patient has complained of pain in her lower right side, just below the costal margin, extending around to the back, sharp and shooting, not in the gall-bladder region. No definite tenderness on pressure. Slight hypersensitivity of the skin. The Pacquelin cautery relieved the pain for a short time.

November 3, 1900. Medical consultation. Patient's respiration rather rapid, superficial. Deep inspiration causes severe pain. No herpes. Pulse 28 to the quarter; no expectoration. Lungs: right side; vocal fremitus is a trifle diminished over the lower right lobe. Throughout the area corresponding to the lower lobe, the percussion note is markedly impaired, extending up as high as the spine of the scapula. Over the lower axillary and subscapular regions, the breath sounds are eufiebbed. A scratching friction rub is just audible. In the apex of the axilla and at the angle of the scapula, the breath sounds have a slight tubular modification. The left lung is clear. No impression recorded.

On November 13, 27 days after operation, the patient was transferred to the medical service. Her wound was well healed; she still had pain and physical signs in the thorax. Temperature 100° F.

On the medical service, a diagnosis of pleurisy with effusion was made. The temperature remained below 100° F. An order was left for her discharge three days after her transfer to the medical department. In preparation for her departure, she was up and dressed at 7 a.m., when she had a sudden collapse and died. Following is the note of the intern: "November 17, 1900. Last night the patient said she was feeling better than at any time since operation. She slept soundly. At 5 a.m. she said she felt perfectly well. She had been discharged the night before and was to leave on the 9 a.m. train. She dressed at 7 o'clock and felt well. A good breakfast at 7:15. She complained of pain around the heart, and a few minutes later said she felt faint. She was put in a chair and laid down. The pulse stopped almost immediately.

We report this case in detail because it is interesting for several reasons:

First, the operation was clean and there was no wound infection; second, there was no evidence of phlebitis; third, it was undoubtedly a case of fatal pulmonary embolism that was preceded by infarction.

We have two such cases in our series, Nos. 8222 and 18,020. Both of these patients had pulmonary infarcts which were unrecognized although the clinical picture was typical. In both cases the patients left their beds while the temperature was still elevated, and in both cases died suddenly. Perhaps they might not have recovered in any event, but we feel that their chances would have been better had they been kept quiet. Our statistics show that all cases of phlebitis are treated carefully and kept in bed, although only 1.5 per cent of them develop embolism. Cases of pulmonary infarction show a mortality of 15 per cent, but do not have the precautions taken with them that they deserve, mainly because they are not diagnosed.

**CASE 2.—Gyn. No. 3492. Atypical pulmonary embolism with abdominal symptoms. Previous infarction. Embolism diagnosed intra-abdominal hemorrhage. Exploratory laparotomy negative. Femoral thrombophlebitis. Recovery.**

A widow, aged 39. Six miscarriages. No children.

**Complaint.**—Tumor of abdomen.

**General Condition.**—Good, except for slight anaemia.

**Diagnosis.**—Myomata uteri, uncomplicated.

*Operation.*—May 11, 1893. Supra-vaginal hysteromyomectomy.

May 18. Sharp pain in left chest, worse on deep inspiration. Temperature 101° F. Friction rub over eighth rib anteriorly. No other positive signs.

*Impression.*—Dry pleurisy.

May 19. Still complains of pain in left chest. Temperature 102°. Pulse 104. Patient has short dry cough.

May 22. Temperature 101° F. Pulse 100. Patient better, has less pain. Straps removed. Friction rub heard. No effusion.

May 24. The signs of pleurisy have disappeared. Temperature 98.5° F. Pulse 80.

May 29. Since the time of the last note, the patient has been improving until this morning, when she was suddenly taken with a fainting spell while sitting upon the chamber. She was at once put to bed and her pulse noted. It was very weak and rapid, rate 120. As soon as the heart had recovered, she commenced to complain of a heavy sensation over the sternum. This increased until 4 o'clock; at this time a thorough examination of the chest disclosed nothing. Pulse 120, feeble and at times almost imperceptible. Strychnin given. At 6 o'clock the patient was seen again; pulse 128, not improved in volume.

Although the symptoms of haemorrhage were marked, it was still felt that there might be some complications in the chest, but another thorough examination of the heart and lungs by the medical chief showed nothing. Preparations were at once made for an exploratory laparotomy. The possibility of a pulmonary embolus was suggested. The symptoms were: Dyspnoea, rapid feeble pulse, rate 140, cold and clammy extremities, action of heart irregular, dark spots in front of eyes, ringing in the ears and a heavy aching pain over the sternum.

The patient was taken to the operating room, anaesthetized with chloroform, and the abdomen quickly opened. The line of first incision was perfectly healed; the second incision was made to the left of the first one. When the peritoneal cavity was opened no trace of haemorrhage was found and no adhesions; everything was apparently in perfect condition. The wound was closed with silkworm gut. The operator now believed the case to be one of pulmonary embolism.

May 31. Pain in the left leg along the femoral vein. Marked tenderness along course of both femoral and popliteal veins.

June 9. Right leg also swollen and oedematous below the knee, not so large, however, as was the left when at its maximum.

June 14. Cervical glands swollen and very painful.

June 16. Pain along course of brachial artery.

June 17. Arm still painful; glands of neck less swollen; right leg almost well.

June 29. Patient discharged. Temperature 99° F.

This case illustrates again the necessity of diagnosing pulmonary infarction. She had been submitted to the operation most frequently associated with phlebitis, infarction and embolism—hysteromyomectomy. After her post-operative rise had subsided, she ran a daily temperature of 100° F. On the eighth day she had her first infarction, the temperature reaching 103° F. on the following day. The infarction was diagnosed as dry pleurisy. After she had recovered from this so-called "dry pleurisy," she was allowed to get out of bed. On the 11th day following the first attack, after the symptoms had disappeared and the temperature had become normal, she had a second and larger embolus that almost proved fatal. It is rather remarkable that this patient survived an infarction, an embolism and two laparotomies, all in less than three weeks, the second laparotomy being performed during the acute collapse following the embolism. The association of

infarction, embolism and phlebitis in one case is rather unusual. We make no apology for presenting the details of this case; she was seen by the chiefs of two departments and is an illuminating example of atypical symptoms in pulmonary embolism.

*Case 3.—Gyn. No. 24894. Atypical pulmonary embolism with cerebral symptoms. Death. Autopsy 5920.*

The patient was a large negro, aged 45. She was admitted in the spring of 1919 and was in good physical condition with the exception of a rather high grade of arteriosclerosis and a blood-pressure of 204/120 (Tyros, ausc.). Temperature 98.6° F. Pulse 92. The urine contained a trace of albumin, but no casts. Because of her hypertension, she was given a period of rest in bed before operation. Her renal function, as measured by the phenolphthalein test and absence of edema, was normal.

*Diagnosis.*—Umbilical hernia.

*Operation.*—Radical cure for umbilical hernia.

*Convalescence.*—Normal, except for a slight elevation of temperature and small serous collection in one angle of the wound. Temperature, 100° to 100.6° F. through convalescence. Temperature on the day before embolism, 100.2° F., pulse 92; on the day of embolism, 101° F., pulse 116; just before death, 102.4° F., pulse 108.

On the 12th day, while the patient was still in bed, she suddenly became dyspneic, markedly cyanotic, with a pulse of 116, and passed into a semi-conscious state, making no complaints of pain or discomfort. When aroused, she answered questions intelligently by nods of the head or a few words, her speech being hesitating and difficult. She almost immediately would lapse back into unconsciousness, breathing rapidly and deeply. She showed marked hyperesthesia, reacting to light touches by general trembling and at times almost mild convulsions of a general type. The left side of her face was slightly drawn, with marked twitching of the muscles of that side. There was no spasticity of the extremities or anisocoria as there was in case No. 7361. Blood-pressure, 145. Lungs clear on auscultation and percussion. By means of oxygen the respiratory rate was lessened and the pulse made slower. While the oxygen was being administered the patient would become very quiet and pass into a sound sleep, the cyanosis disappearing more or less. After the oxygen mask was removed, she would soon revert to her former condition. After 18 hours, she died.

*Autopsy 5920.—Anatomical Diagnosis:* Pulmonary embolism. Edema of lungs. Arteriosclerosis. Infarct of spleen. Bilateral fibrinous pleurisy. Myoma of uterus, small.

The operative incision had healed *per primam*, except for a small collection of fluid in the fat.

*Heart:* The pericardium contains 100 c.c. of clear fluid; except for few old adhesions it is negative. Heart hypertrophied, weighing 540 grams. Endocardium smooth, valves clear. Muscle negative. Right ventricle contains a small true venous thrombus.

*Lungs:* A large number of small emboli in pulmonary arteries of both sides. Lungs everywhere crepitant, air containing, no areas of consolidation. No bronchopneumonia.

*Brain:* Negative.

*Source of embolus:* Not determined.

*Case 4.—Gyn. No. 13296. Simple pulmonary infarction. Recovery.*

A colored woman, aged 38 years, admitted to The Johns Hopkins Hospital, November 9, 1906.

*Complaint.*—Tumor of lower abdomen, first noticed 13 months before admission. General condition excellent. Well nourished. Temperature 98.6° F. Pulse 80. Lower abdomen and pelvis filled with a fibroid arising from the fundus of the uterus.

*Operation.*—October 10, 1906. Hysteromyomectomy, double salpingo-oophorectomy. No unusual complications.

*Post-Operative Convalescence.*—After the first week, the patient settled down for a normal convalescence, on full diet, the bowels moving regularly, with no complaints and no pain. Temperature on the seventh day, 100.2° F. Pulse 118.

October 20. Wound dressed, healed *per primam*, clean. Abdomen everywhere soft. General condition excellent. Temperature still rising to 100° or 101° F. every afternoon, pulse 90 to 100. No reason for fever found.

October 24. Patient up in chair to-day for first time. Convalescence still uninterrupted, except for slight elevation of temperature, 99.6° to 100° F. to-day.

October 26. The patient today complains of sharp pain in the left side of the chest, near the base, also anteriorly over the lower part of the sternum. Breathing difficult, the patient being forced to take numerous short breaths because of pain. Examination of chest showed upper fronts and backs apparently clear. Suggestive dulness at bases on both sides in backs, not definite. No râles, no friction rub. W. B. C. 21,800. Temperature 100.4° F. Pulse 108. (See temperature chart, Fig. 3, page 103.)

October 28. Patient no better this morning. Dyspnea. Severe pain on inspiration. Temperature 102° F. Pulse 124. Respiration 48 to 58. During the last 24 hours the patient has been expectorating a frothy, slightly tenacious, mucoid, blood-stained sputum, about 1½ ounces in 24 hours. Examination of chest shows definite dulness in lower back on left side, with tubular breathing over a small area. Friction rub not definitely heard. Abdomen soft, No tenderness. Wound healed. Morphin has been necessary during the past 48 hours. W. B. C. 16,8000.

October 30. Patient much better to-day. Slight dyspnoea, but still expectorating very small amounts of bright red, blood-stained, frothy sputum, about half an ounce in 24 hours. Temperature 100.4° F. Pulse 102. Respiration 24 to 30.

October 31. Condition about the same. Patient says that constant cold applications to the left back and over the heart make pain less. Takes liquid nourishment well. Very little sputum. Examination of sputum for tubercle bacilli, negative. Temperature 99.6° F. Pulse 96. Respiration 24 to 32.

November 1. Patient had a very good night. Temperature not above 98.6° F. since 8 a. m. to-day, pulse 80 to 86, respirations 24 to 28. Has no pain in side, except on taking a deep inspiration or moving about. Examination of left chest shows dulness of percussion note at base with tubular modification of breath sounds. Morphin discontinued. Sputum negative for tubercle bacilli.

November 2. General condition improving. Patient comfortable. Temperature 99.2° F. Pulse 92. Respirations 24.

November 3. Patient doing very nicely. W. B. C. 10,000. Sputum negative for tubercle bacilli.

#### DISCUSSION

These notes are extracted practically verbatim with some abbreviations from the history of this patient. Her further course was uninterrupted. She had an occasional slight pain in the left side of her chest for a week or more after the last note made above. Her sputum and cough disappeared entirely. There was some impairment of the percussion note and the breath sounds were slightly roughened until the end of the third week after the infarction, showing the time necessary for complete resolution. There was also a slight elevation of the temperature at times, running up to 99.4° or even 100° F. occasionally. On the 19th day after her infarction she was allowed to be up in a chair for the first time and was discharged on the 25th day. She had no pain or swelling of the legs at any time. The temperature chart of

this patient during the acute symptoms of the infarction is found earlier in the article (page 103) showing the difference between it and a typical post-operative bronchopneumonia.

CASE 5.—*Gyn. No. 12587. Pulmonary infarction, multiple abscess formation. Death. Autopsy 2651.*

Patient, a rather sick colored woman, aged 39. Admitted to hospital December 30, 1905.

*Complaint.*—Tumor in the abdomen, nausea and vomiting. Married seven years, no pregnancies. Abdomen irregularly enlarged by a hard nodular mass rising from pelvis to level of umbilicus. Slightly tender over McBurney's point. Pelvis choked by this large tumor. Lungs clear on auscultation and percussion.

*Diagnosis.*—Myomata uteri.

Temperature 97° to 98.5° F. Pulse 100. Respirations 24. Hb. 70 per cent. Urine contains a few coarse and finely granular casts, with a trace of albumin.

*Operation.*—January 3, 1905. Hysteromyomectomy. Double salpingo-oophorectomy.

Tumor very vascular, bound down by many vascular adhesions. Pulse during operation 140 to 150. Ether well taken.

*Post-operative Notes on Convalescence.*—January 4. Patient left operating table yesterday in rather poor condition. Pulse 148. Temperature normal. Respiration 26. Not much nausea or vomiting. Received subcutaneous salt infusion on operating table. During afternoon, pulse became weaker and more rapid, requiring stimulation with digitalis, strychnin and proctoclysis. Pulse to-day stronger and slower, rate 128, respiration 28, temperature 98.4°, rising to 99.8° F. in the afternoon. Taking fluids well. Conditions improving.

January 5. Patient's condition has improved markedly, pulse slower and stronger, rate 120. Strychnin discontinued. Bowels moved by enema. Has voided. Temperature 100° F. Respirations 24.

January 6. Last night at midnight patient complained of pain in her left chest. No cough. Temperature at that time 100° F., pulse rose to 136, respirations to 32. About an hour later she began to develop a slight cough, apparently dry and unproductive. By noon to-day, the temperature was 102.6° F. Pulse 160. Respirations 32. W. B. C. 30,600. On examination at 2.30 p. m. the patient looked ill. Pulse small and running. Slight dilatation of alæ nasi. Sordes on lips. No evident cyanosis. Chest: Right front and axilla clear on percussion. Occasional fine râle in lower axilla. Left side: marked tympany over and above clavicle merging with cardiac dulness. Also tympany at apex of left axilla. Elsewhere resonant. On auscultation, definite tubular breathing over left upper front. Breath sounds rather harsh at apex of axilla. Everywhere numerous rather coarse moist râles on inspiration and expiration. Just at anterior axillary fold a to-and-fro pleural friction rub can be heard.

On the left side behind, there is dulness over the upper portion from apex to midscapula. The note is nowhere flat, but has a tympanitic quality. Numerous fine dry râles over left upper back. Breath sounds nowhere tubular or especially harsh. If anything, vocal fremitus and vocal resonance are diminished over impaired area.

The patient does not seem toxic. A rather severe grade of abdominal distension has developed. Given turpentine stapes and enemata for distension; stimulant, and heroin and codein for thoracic pain.

January 7. Towards evening yesterday, the patient grew worse. Pulse remained around 160 and of poor quality. She responded poorly to stimulation. By midnight her condition was alarming. Temperature 104.4° F. Pulse 160. Respirations 52, labored with an expiratory grunt. Coughing rather frequently without appar-

ently producing anything. (No haemoptysis noted.) Abdominal distension severe and intractable.

Physical signs unchanged in lungs. Given salt solution by hypodermoclysis, rather active stimulation and morphin. Patient seemed to respond well. The physician felt justified in leaving the ward. Fifteen minutes later, however, her respiration suddenly became more labored and gasping, her pulse practically imperceptible. Emergency measures were instituted without avail. She died at 5.25 a. m.

*Autopsy 2651.—Anatomical Diagnosis:* Operative wound, mid-line (hysterectomy for myoma) drainage wound in vagina. Acute fibrinous pelvic peritonitis. Thrombosis of uterine and vesicle veins. Embolism of pulmonary arteries. Lung abscesses and broncho-pneumonia. Acute bronchiectasis and bronchitis. Acute fibrinous pleurisy. Acute diphtheritic colitis. Cloudy swelling of the viscera.

*Lungs:* The left lung shows some fresh tags of fibrin over the anterior portion of the upper lobe. It shows a raised, firm area, quite airless, measuring roughly 5 cm. in diameter. Below this is a collapsed purplish area close to the margin of the lung, of doughy consistency. The lymph nodes are large and deeply pigmented, but show no caseous foci. The pulmonary arteries are clear at the hilum, but the smaller branches show numerous plugs loosely adherent to their walls, some of which can be removed easily, others with considerable difficulty. Some of the adherent ones are long and are like angleworms in appearance, resembling exactly the plugs found in the vesicle veins. The pulmonary vein is clear.

The larger bronchi show intense injection and purplish puffy mucosa. The smaller bronchi leading to the collapsed portion in the upper lobe are diffusely dilated along their course, out to within 0.5 cm. of the pleural surface, and contain a purulent material. Their walls are intensely injected.

The cut surface shows the large area of consolidation mentioned before to be airless and granular, of a grayish color, showing here and there softened areas up to 0.5 cm. in diameter, with an injected zone and a soft grayish center. The vessels here all show their lumina closed by ante-mortem clots. Most of the lung tissue is of a moist pinkish-red color and air-containing, dotted over thickly by these areas of consolidation with a zone of intense injection and central softening. The lower lobe shows a less extensive change, is voluminous, but shows here and there a small abscess.

The right lung is voluminous. Its artery shows many plugs of ante-mortem type. There appears to be no definite area of consolidation, except in the upper lobe, where there is a small area the size of a pea whose center is beginning to soften. The rest of the lung tissue is moist and deep red in color. The bronchi show intense injection throughout.

*Microscopical Examination:* The vessels show numerous emboli made up of fibrin, red and white blood cells. Some of these emboli show many fibroblasts at their margin and were evidently beginning to organize in the vessels where they were formed. There are many smaller and larger abscesses with complete softening of the lung framework. Some of the alveoli are packed with leucocytes and there is very little fibrin to be seen anywhere. In other places the alveoli contain much serous fluid and only an occasional cell. The bronchi, as a rule, show considerable injection, their lumina being full of leucocytes. There are some areas where there has been necrosis of lung tissue around large clumps of bacteria.

*Pelvic Organs:* The stump of the cervix is very much injected and closed in by catgut sutures. Some of the large veins on both sides of the cervix are tied by catgut ligatures and are thrombosed. From these veins there is an extension of the thrombosis to the much dilated veins around the base of the bladder. These vessels contain organized branched thrombi which are easily withdrawn from the lumina of the vessels.

*Heart:* Valves normal. Muscle normal in appearance. Microscopically normal.

#### DISCUSSION

We present this case to illustrate two main points: (1) The clinical history; and (2) the short course, due to severe complications.

1. The clinical history reveals a typical picture of pulmonary infarction, with one exception. It occurred on the fourth day of convalescence. This is rather early, as most of our cases occurred during the second or third week. Again, this patient had no haemoptysis. To many of us, the presence of haemoptysis has always been the cornerstone on which the diagnosis of pulmonary infarction rests. Our statistics show that just about one-third of our patients had hemorrhagic sputum. In this case there was no pain or swelling of the leg. The thrombosis was entirely limited to the pelvic veins.

2. The short course that this case ran before death is rather unusual for pulmonary infarction. The onset was not very severe, there was no marked collapse, no cyanosis at the beginning. The patient apparently had many repeated small infarctions during the short period she lived. Autopsy showed that there were no large embolic masses, none of sufficient size to occlude a large vessel in the pulmonary system.

It seems that her rather sudden death was due to four factors complicating the infarctions. The poor condition of the patient before operation; a serious grade of operative surgical shock from which she was just beginning to recover; abdominal distension attending the pulmonary condition; severe infection of the infarcts. The poor condition of the patient before operation made her an easy prey to complications. She was just recovering nicely from the shock of the operation when the first infarction occurred. Abdominal distension almost immediately reappeared and became marked and uncontrollable. We have already called attention to the occurrence of abdominal symptoms in connection with embolism and infarction.

When to all these unfavorable factors was added the development of abscesses in the infarcts, the combination was fatal and the end came soon. Here again it is impossible to say whether the emboli were primarily septic in type, or whether they were bland and the infarcts merely furnished a good culture medium for the growth of organisms already present in the lung. It is probably true that early in convalescence the lungs are not as resistant to infection as they are after the congestion and irritation of the ether have worn off. In this connection it is instructive to note that half of our patients with infarction that died of either lung abscess or gangrene developed their infarctions during the first six days of convalescence.

CASE 6.—*Gyn. No. 17670. Pulmonary Infarction, followed by pulmonary gangrene. Death. Autopsy 3585.*

Patient a well-nourished negress, aged 24. Had had two children. Admitted to hospital, July 26, 1911. Operated upon July 29, and died August 14, 1911. General condition excellent. Temperature 99.2° F. Pulse 80. Urine negative.

*Complaint.*—Pain in abdomen. Profuse and irregular menses.

*Diagnosis.*—Chronic appendicitis. Metrorrhagia.

*Operation.*—July 29. Appendectomy. Dilatation of uterus and curettage. No unusual findings at operation. Appendix very adherent. Pelvic organs normal, except for slight enlargement of the uterus. Endometrium normal. Condition of patient at end of operation good.

*Convalescence.*—July 30 convalescence good. Slight distension, relieved by rectal tube. Temperature 100.8° F. Pulse 120.

July 31. General improvement. Liquid diet. Temperature 99.8° F. Pulse 116. Urine examination essentially negative.

August 1. Patient comfortable. No untoward symptoms. Bowels moved. Has been voiding well. Temperature still remains, however, between 99.5° F. and 100° F. Pulse 110.

August 2. First dressing. Wound clean, stitches removed. Complains of pain in left hypochondrium. Temperature 99.6° F. Pulse 110. Respiration 24. Physical signs negative.

August 3. Patient is having severe pain in left lower axilla, radiating through to left back. Pain is knife-like, worse on sudden or deep inspiration. Respiration shallow, rapid, restricted slightly over lower left thorax. Considerable dilatation of alæ nasi. Pulse rapid, full, bounding, 130 to minute. No cough. On examination of chest, percussion note seems unimpaired over both sides of chest. Vocal fremitus apparently increased in lower left axilla. Breath sounds suppressed in lower left axilla and below angle of left scapula. No tubular breathing, no râles heard, no friction rub. Temperature 101° F. Pulse 128. Respirations 38 to 42. W. B. C. 18,000.

August 4. To-day for first time the patient has been coughing, with occasional scanty expectorations of blood-streaked sputum. Cough is dry, harsh and painful. Over the left base there is slight impairment of the percussion note and at the end of inspiration many clicking râles can be heard. Expiration is harsh but not much prolonged. W. B. C. 24,000. Temperature 101.6° F. Pulse 120. Respiration 28 to 36. Sputum negative for tubercle bacilli.

August 6. Temperature 103° F. Pulse 120. Respiration 32 to 40. Profuse bloody expectoration. Quite marked cyanosis and respiratory distress. Percussion note is slightly dulled over upper left front, definitely flat over lower front, axilla and left back, below the angle of the scapula. Breath sounds are very harsh and accompanied by many sonorous râles, chiefly expiratory in time. There is a small area of tubular breathing, about the size of a silver dollar, in the back at the angle of the scapula. Below the breath sounds are very distant and transmission of the voice sounds is diminished. Heart, as before, not much dilated. Prolonged second sound of good quality. Sputum negative for tubercle bacilli.

August 7-8. Temperature 103.4° F. Pulse 136. Respirations 42. Condition about same, except that at times she is more comfortable. Cyanosis and dyspnea still marked. Physical signs about the same. Sputum contains no tubercle bacilli, but many chains of cocci and diplococci.

August 10. Condition much improved. Temperature lower, 101.4° F. Pulse still rapid, 140 to 150. Respirations 32 to 42. Patient comfortable. Dyspnea still marked. Pulse strong and regular though rapid. Profuse bloody expectoration continues. Examination of sputum reveals no tubercle bacilli, no elastic tissue. Physical signs essentially unchanged.

August 11. Temperature less elevated. Pulse continues rapid, is irregular. Respirations 40. Marked cyanosis at times with great respiratory distress. General condition, however, seems improved. Physical signs about the same—dulness over left front, flatness in left axilla and lower left back. Breath sounds harsh, accompanied by many dry and bubbling râles. Small area of tubular breathing at angle of scapula. Breath sounds and transmitted voice sounds are diminished or almost absent in left axilla.

Vocal fremitus also absent over this area. Profuse bloody expectoration, rather frothy. No odor. Temperature 102° F. Pulse 130 to 155. Respiration 40.

August 13. Condition yesterday and to-day shows no improvement. This afternoon a peculiar nauseating sweetish odor was observed on the patient's breath and from the sputum. No gross masses in sputum, which is dark bloody. This evening, the temperature, which had fallen during the day to 99.8° F., rose a degree, the pulse became very rapid, 160 to the minute, weak, irregular, and finally could barely be felt at the wrist. Respiratory distress marked, rate 40, shallow, with expiratory grunt or groan, and marked cyanosis. On the left side of thorax there is marked restriction of respiratory movements, the lower ribs being held practically immobile. Vocal fremitus absent over lower axilla and back. Marked pulsation synchronous with heart beat, extending far out into the left axilla almost to the angle of the scapula behind. Other physical signs essentially the same.

An exploratory puncture with a fine needle was performed in the eighth interspace below the level of the scapula; pure dark blood was obtained. A thoracentesis was then done, and 200 c. c. of dark bloody fluid were obtained.

There is considerable abdominal distension.

August 14. The patient died to-day.

*Autopsy 3585.—Anatomical Diagnosis:* Operation, appendectomy, dilatation and curettage of the uterus. Bronchopneumonia, bilateral. Gangrene of base of left lung with cavity formation and terminal hemorrhage. Acute hemorrhagic pericarditis. Acute fibrinous pleuritis. Acute fibrinous perisplenitis.

*Thorax:* When the thorax is opened the left pleural cavity is found to be obliterated by fine fibrinous adhesions. The apex is free. On separating these adhesions a large hole containing about two liters of dark blood-stained fluid is found in the base of the lung. This blood-stained fluid has a very offensive odor. On opening the pericardial sac, a small excess of blood-stained fluid is found and a hemorrhagic exudate is found over the region of the left ventricle.

*Heart:* Normal size, 240 grams, epicardial surfaces everywhere normal. Right auricle filled with fluid blood. Surface smooth. Valves delicate, smooth. Right ventricle normal. Pulmonary valves delicate. Root of pulmonary artery normal. Left ventricle moderately filled with fluid blood. Endocardium smooth. Valves delicate, smooth. Aorta smooth, elastic. Heart muscle normal.

*Lungs:* Base of left lung is occupied by a large, ragged, worm-eaten cavity containing the above mentioned fluid. There are shreds and tags of tissue running through the cavity. On removal of the lung, the gangrenous area described measures 12 cm. in diameter. No lesion of the arteries is to be made out in gross, except at the apex. The lung is plastered over with a rather thick, fibrinous pinkish-colored exudate. This is rather easily torn away. The lobes are glued together. The lung is kept intact for injection of the blood-vessels.

On injection of the arteries after ligating the veins, there is found to be a general oozing as from a sieve. No definite rupture of an artery or vessel could be demonstrated. On section, the upper lobe is pale, pink in color, moist and everywhere crepitant. The lower lobe, on section, is firm, moist, of a rather dark grayish-red color, shading off at the base into gangrenous shreds and tags composing the wall of the cavity described. One small artery is found to contain a fresh thrombus. The other vessels are negative. The structures at the hilum are normal, except for slightly enlarged pigmented glands.

The right lung is fairly voluminous, of a pale gray color, mottled with hard, raised, pinkish-brown areas. The structures at the hilum appear quite normal except for the glands which are slightly enlarged and of a gray color mottled with black coal pigment. The upper lobe on section is pinkish-gray color, rather moist, and everywhere crepitant. The middle lobe is crepitant only in

small areas. The rest of the lobe is voluminous, nodular, firm, very moist and of a pinkish-gray color. The cut surface shows irregular raised areas which are firm, not containing air. The lower lobe likewise feels nodular and shows a few dark areas projecting upon the surface. On section, the lung shows irregular raised nodules of darker red lung tissue, not containing air. No abscesses are found throughout the lung.

*Origin of Thrombi:* The pelvic veins show no thrombus masses.

*Culture of Thrombus or Abscess:* Not reported.

#### DISCUSSION

This case is presented in detail for three reasons:

(1) It gives the clinical and pathological picture of a type of pulmonary infarct with a very serious complication—infestation. Whether the abscess formation and gangrene came as the result of an infected embolus or whether they were due to a bland embolus lodging in an infected lung, is sometimes a difficult and usually a purely academic question. In this case, the absence of pulmonary symptoms and signs before the infarction, and the occurrence of the infarction on the fifth or sixth day might lead one to believe that the infection was transported to the lung with the embolic material. On the other hand, a patient who has had an ether anaesthetic and has been in bed continuously for a week might very well have a certain amount of hypostatic congestion of the lower lobes of the lungs and an inactive low-grade bronchitis. Given such conditions as this, the addition of a good culture medium like a fresh infarct makes the opportunity for activation of the infection favorable indeed.

(2) This case shows, moreover, the difficulty of establishing a clinical diagnosis unless the history of onset is considered. After development of the abscess and gangrene, the clinical picture of infarction is wholly lost. The infected lung is drained by its bronchus; and the aspiration of the infected material from this lobe into others soon gives rise to patches of bronchopneumonia which complicate the original picture.

(3) The difficulty attending the diagnosis of pulmonary embolism and infarction on the autopsy table is also brought out by this post-mortem examination. Emboli are frequently not fixed; they are often loose in the pulmonary artery. Hence they must be searched for *in situ* before the organs are removed. After a certain length of time, emboli may become liquefied. This applies particularly to small particles such as would cause infarcts. Infection would also tend to hasten liquefaction. In this case in particular, while only one small thrombus was found, the pathologists expressed the opinion that the cause of the pulmonary complication was undoubtedly infarction.

**NOTE.**—We wish to express our indebtedness and thanks to Dr. Howard A. Kelly and Dr. Thomas S. Cullen for their kindness and suggestions to us in the preparation of this paper. The medical department, also, has always shown us the greatest courtesy in giving us the benefit of consultation. This has been utilized in practically all the pulmonary cases. To the department of pathology we are indebted for free access to the records of all our cases that were examined at autopsy.

For the benefit of any who might in the future care to examine this subject in greater detail, we shall herewith give

the list of the cases on the basis of which this report has been made. The 34 cases which we have diagnosed pulmonary infarction are as follows, the designations referring to the gynaecological numbers in the Johns Hopkins Hospital: 8222, 4902, 3492, 4955, 6659, 660, 7534, 7996, 10653, 11060, 13908, 13354, 17253, 16960, 18375, 8764, 10204, 10569, 12287, 12663, 16250, 13296, 14369, 19697, 21083, 1004, 13340, 17670, 1576, 19810, 21562, 12587, 20338, 24747. Of these 34 patients, the following died: 8222 (autopsy refused); 1004 (autopsy No. 304); 12587 (autopsy No. 2651); 13340 (autopsy No. 2801); 17670 (autopsy No. 3585).

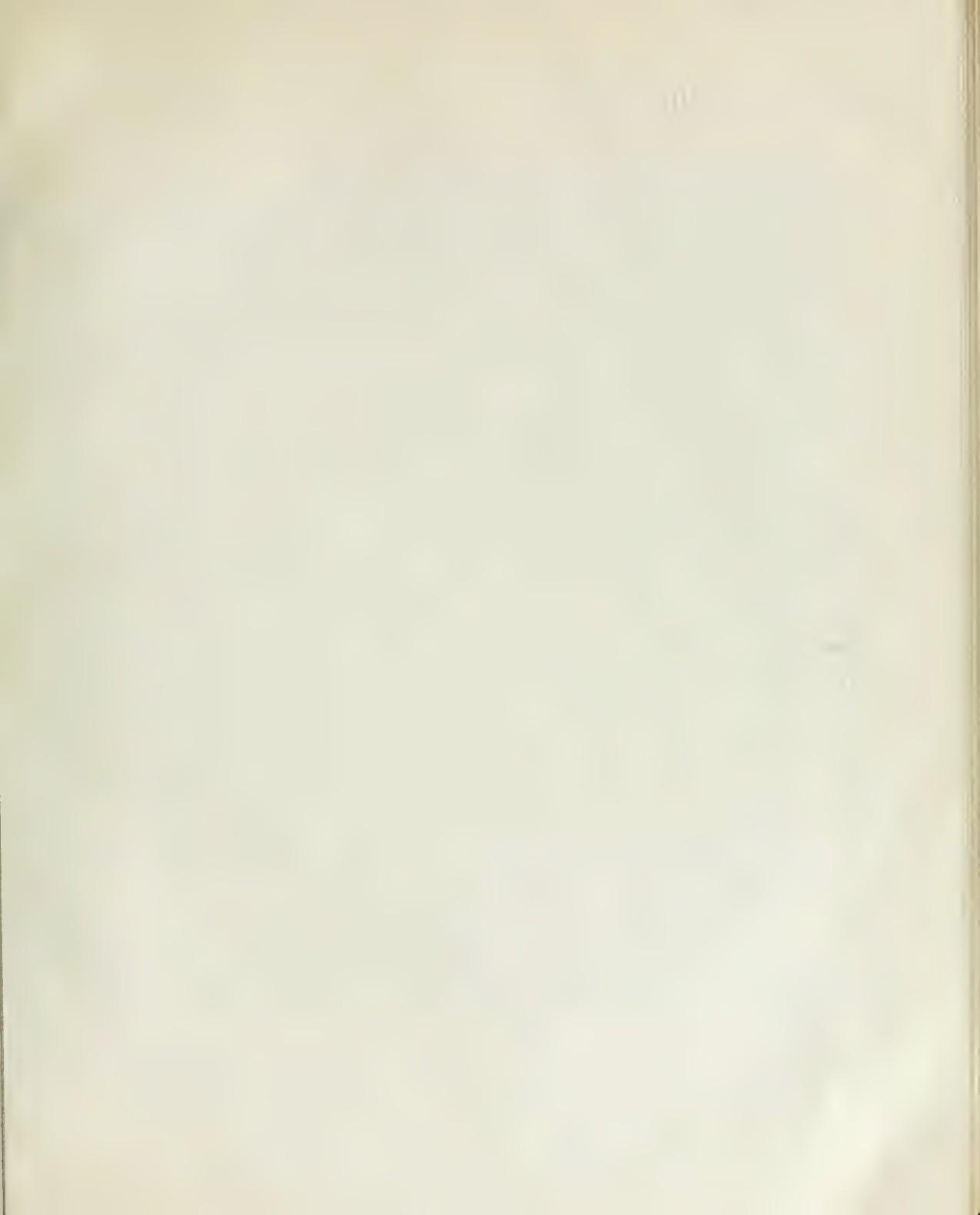
The cases of fatal pulmonary embolism which we have included are as follows:

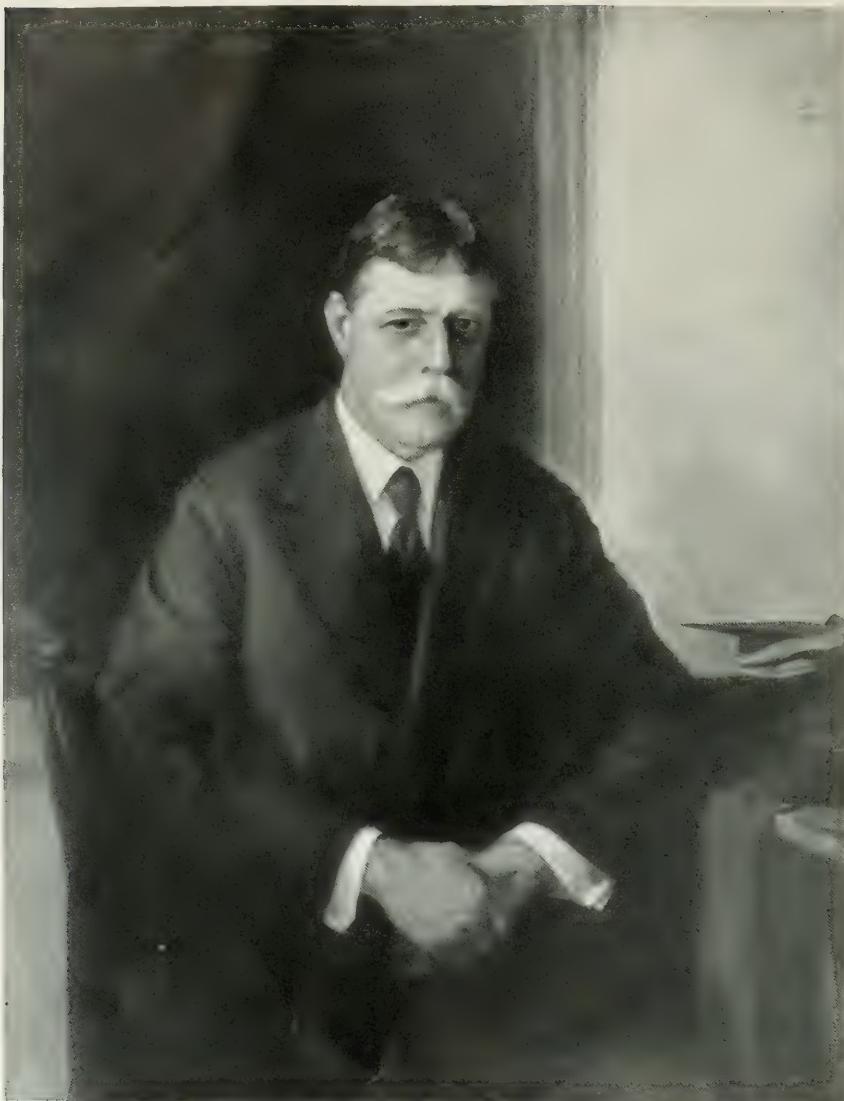
Gynaecological number	Autopsy number
24894	5920
20709	4223
21375	4413
22338	4790
76	54
2492	486
6939	1374
24747	5869
7361	1445
8713	1733
16840	refused.
17503	3553
18020	3659
19872	4037
19006	3864
23670	5432
25390	refused.
8222	refused.
13340	2801

There were four cases of pulmonary embolism with previous pulmonary infarction, Gyn. Nos. 8222, 13340, 3492, 7996. Of these, the first two resulted fatally and are included in the above list.

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## PRESENTATION TO THE UNIVERSITY OF THE PORTRAIT OF DR. JOHN WHITRIDGE WILLIAMS

*Mr. President, Members of the Board of Trustees, of the Faculty, and Alumni of the University, Ladies and Gentlemen:*

In behalf of the donors I have been requested to present to you the portrait of Dr. John Whitridge Williams. The donors of this portrait are the graduates of the medical department of the university. Already no less than two-thirds of these graduates have subscribed, their subscriptions being accompanied with warm expressions of appreciation of the services of Dr. Williams—a remarkable tribute to him I venture to say.

The painter of this portrait is Mr. Wayman Adams, a young artist of Philadelphia, whose work is already most favorably known, an artist of established and increasing reputation.

Dr. Williams was graduated in arts from this university in 1886 and in medicine from the University of Maryland in 1888, just one year before the Johns Hopkins Hospital was opened. After a short period of foreign study he became connected with the hospital first as an assistant to Dr. Kelly in the department of gynecology, and later on the obstetrical service of the hospital, of which he was placed in charge and has remained in that capacity until this time. The entire organization and development of the department of obstetrics both in the hospital and in the medical school is his work. It is not a little remarkable, I think, inasmuch as the Johns Hopkins Hospital was designed from the beginning to serve the needs of the medical school as a teaching hospital, that no provision was made for the care of obstetrical patients. It

is only now that a new building, the funds for which are contributed by an anonymous and most generous donor, is to be erected to provide for the obstetrical department. Dr. Williams has developed his service and his teaching under not inconsiderable difficulties and obstacles. Therefore, the results which he has obtained are the more creditable to him, and to the medical school; and I may say too that the contributions which he has made to his subject are the more remarkable in view of the handicap under which he has worked.

Dr. Williams was born and bred in Baltimore—a member of a family well known in the social and professional circles of this city. Where so many of us were imported from the outside it is no small satisfaction that we found here one who has served the university so faithfully and brought such distinction to the hospital and to the university.

An admirable teacher—an important contributor to his subject! This is not the occasion to indicate the value and extent of these contributions. It must suffice to say that they are recognized the world over—his text-book, the recognized one in this country, is used to no small extent on the other side of the water.

He has been an important influence in the medical department. Always a sympathetic friend to the students of the university, it is not surprising that they should have been so ready to contribute toward the perpetuation of his memory in this portrait. It is fitting, I think, that the portrait should be presented at this time, when the difficulties under which the department of obstetrics has labored are about to be, to a large extent, removed, when after these many years of effort

and struggle the department is placed upon a secure and admirable basis. Himself an advocate of what we call the university full-time system of teaching in our medical school,—Dr. Williams' department will now be reorganized on the full-time basis, the funds for which are generously donated from the same source from which the original endowment came, the General Education Board.

It is a special privilege for me, and I am sure it is a source of great satisfaction to all of his colleagues in the medical faculty, and in the university, to be able to present this

portrait of one who, in his later years as dean of the medical department of the university has contributed so loyally, so devotedly, so unselfishly of his time and work to the university. An admirable teacher, a loyal supporter of the best academic ideals, a friend of the students and of the alumni, a real ornament to the university, Dr. John Whitridge Williams.

NOTE.—Stenographic notes of remarks made at the Commemoration Day Exercises, February 23, 1920, by Dr. William H. Welch, but not revised by speaker.

## THE FATE OF BACTERIA INTRODUCED INTO THE UPPER AIR PASSAGES

### IV. THE REACTION OF THE SALIVA

By ARTHUR L. BLOOMFIELD and JOHN G. HUCK

(From the Biological Division of the Medical Clinic, The Johns Hopkins University and Hospital)

One of the most important phases of recent work in bacteriology has been the attempt to study and define more clearly the exact conditions underlying the growth of micro-organisms. Whereas in the early years of microbiological study such conditions were for the most part regarded as being relatively crude, it is now known that in the case of many pathogenic bacteria a subtle combination of circumstances is essential not only for optimal growth, but even for the initiation of any growth. Failure of some workers to isolate influenza bacilli during the recent epidemic was clearly due to the faulty methods, because very slight variations in the composition of the media may make all efforts unsuccessful, and similar precautions are necessary in growing in the most advantageous manner the pneumococcus, meningococcus, gonococcus and other organisms.

Of the many qualities which are essential to a favorable environment for bacterial growth one of the most important is the proper hydrogen-ion concentration of the medium. Much work has now been done which shows conclusively not only that growth ceases when the reaction of the medium passes beyond certain limits, but also that a definite pH is necessary for the initiation of growth. Clark and Lubs<sup>1</sup> review the literature on this subject up to 1917 and point out its bearings in connection with the growth of the members of the typhoid-colon group, streptococci, yeasts and moulds. Avery<sup>2</sup> recently has studied in detail the reaction limiting the growth of streptococci and pneumococci. He emphasizes the importance of distinguishing between the final hydrogen-ion concentration, that is, the point at which growth stops in the culture—and the limiting reaction or pH above which growth cannot be initiated. In the case of the pneumococcus for example, it was found that growth once initiated continued until a reaction of pH 5.0 had been reached, but that growth could not be started in the same medium if its reaction were more acid than pH 7.0. The exact manner in

which the multiplication of bacteria is influenced by the pH of the environment is uncertain, but observations on the relation of acidity to enzyme action and on the physical condition of colloids (see Clark and Lubs) are suggestive.

In studying the fate of organisms introduced into the upper air passages<sup>3</sup> it was found that certain bacteria disappeared very rapidly, the explanation apparently being that conditions were relatively unfavorable for growth and that the organisms were therefore washed away more rapidly than they multiplied. It seemed possible that the reaction of the saliva might be of importance in favoring or inhibiting bacterial growth. The following observations were therefore collected as a preliminary to test-tube experiments on the effect of saliva of various reactions on the growth of bacteria:

#### THE MOUTH AND NASAL SECRETIONS

Without attempting to enter into in detail the physiology and chemistry of the mouth and nasal secretions a few points of importance in the present connection may be recalled. The saliva as found in the mouth is a mixed secretion derived from the salivary glands and from the small glands situated in the lips, palate, tongue, sublingual space, and pharynx. To this may be added the nasal secretions which drain back into the pharynx through the posterior nares. This composite secretion is both serous and mucous and varies constantly and is influenced by a variety of conditions, at times being a profuse colorless or opalescent thin fluid and again a more viscid, thick material. The acts of swallowing and expectoration in conjunction with the stimuli of food, drink and irritants, lead to a constant production and flux of these mouth fluids. Among the important constituents of the saliva may be mentioned fermenters such as ptyalin and maltase, traces of protein, mucin, and inorganic salts—chlorides, phosphates, carbonates, and sulphates. The carbonates are very abundant and may be important in connection with the reaction of the saliva.

There is also much CO<sub>2</sub> in solution. Potassium sulphocyanid present in small amounts has been thought by some writers to have an antibacterial action. The reaction is weakly alkaline to litmus.

We have been unable to find in the literature any detailed study of the reaction of the mouth secretions under various conditions. Michaelis and Pechstein<sup>4</sup> in another connection report a few observations. Six specimens of saliva were found to have a pH respectively of 6.79, 6.91, 6.92, 6.65, 6.34, and 7.01. The first three observations were made on undiluted saliva, the last three on saliva diluted one to ten with water. The tests were made by the electrometric method.

#### METHODS

The individual to be examined was requested to gather a mouthful of saliva. By churning the secretion in the mouth a composite mixture was obtained. This was expectorated into a graduate and immediately centrifuged at high speed for five minutes to throw down gross particles. The clear supernatant fluid was then decanted. One cubic centimeter of this was measured into a standard test-tube and 9 c.c. of freshly distilled water were added. The proper amount of indicator was introduced, the contents of the tube mixed by rotation and the reading made by comparison with a set of standard tubes of different pH. The indicators used were phenolsulphonphthalein and alizarin, covering respectively the range from pH 8.3 to pH 6.6 and pH 6.6 to pH 5.0. Four drops of .04 per cent solution of phenolsulphonphthalein and one drop of .2 per cent alizarin to 10 c.c. of the standard and of the test mixture were found to give the best color differentiation in this work. The test mixtures with this technique gave a clear limpid fluid which could be readily and accurately compared with the standard tubes. The readings were always made within 15 minutes of the collection of the specimen.

#### TECHNICAL CONSIDERATIONS

1. *Glassware.*—The same set of glassware—test-tubes, centrifuge tubes, pipettes, and graduates was used throughout the work. It came in contact with no alkali, acid, or strong chemicals which might have influenced the readings. Immediately before use it was thoroughly rinsed with freshly distilled water.

2. *Water.*—Freshly distilled water was used in all the tests for diluting the saliva. Its pH was usually 6.0 to 6.2.

3. *The Standard Solutions.*—The standard solutions were freshly prepared every two weeks from buffer mixtures supplied by the chemical laboratory of the medical clinic.

The technique was furthermore checked in various ways.

4. *The Effect on the pH of the Saliva of Contact with Air.*—Inasmuch as the saliva contains a considerable amount of CO<sub>2</sub> it was necessary to determine the alteration in reaction resulting from the specimen standing in contact with the air. Specimens were collected and one part was immediately covered with paraffin oil. The remainder was placed in a tube in contact with the air. The pH of both specimens was determined after various intervals (Table I).

TABLE I.—EFFECT OF CONTACT WITH AIR ON THE pH OF SALIVA

Specimen	pH immediately after collection	pH after standing in contact with air		pH after standing under paraffin oil	
		20 min.	60 min.	20 min.	60 min.
B	6.6	6.6	.....	6.6	.....
B	6.7	6.7	6.8	6.7	6.7
S	7.0	7.0	7.0+	7.0	7.0
D	6.2	6.2	6.3	6.2	6.2
B	6.9	6.9	7.1	6.9	6.9

These observations show that the pH of the saliva was not appreciably altered by twenty minutes contact with the air. In doing the tests readings were always made within this length of time from the collection of the specimen.

5. *The Buffer Value of the Saliva.*—To obtain clear suspensions of saliva it was found necessary to dilute the expectorated material with nine parts of water. Tests were made to determine if the saliva contained enough buffer salts to allow such a dilution. Distilled water containing the proper amount of indicator was added to the saliva until there was a noticeable change in color. The buffer value for 1 c.c. of various specimens of saliva in terms of distilled water is shown in Table II.

TABLE II.—BUFFER VALUE OF SALIVA

Specimen	pH	Buffer value for 1 c.c. in terms of distilled water	pH of water
B	7.1	22 c.c.	6.0
H	6.7	20 c.c.	6.0
M	7.1	20 c.c.	6.0
C	6.9	20 c.c.	6.2
B	6.9	16 c.c.	6.2
B	6.1	35 c.c.	5.6
L	6.4	25 c.c.	6.0
D	7.1	25 c.c.	6.2

It is apparent that the saliva contains enough buffer substances to allow a dilution of 1:10 without altering the reaction.

#### RESULTS

*Normal Individuals.*—One hundred and two observations were made on 52 clinically normal individuals during a period of about two months. The specimens were collected at various

TABLE III.—REACTION OF SPECIMENS OF SALIVA FROM HEALTHY PEOPLE

	pH	6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3
Number of specimens.....	.....	2	2	3	3	2	7	19	7	8	18	16	12	1	1

times during the day and at night without particular reference to the intake of food or fluid, smoking, or cleaning the mouth. It was desired to cover all possible normal variations in the condition of the mouth. As may be seen in Table III,

the reaction of 80 per cent of the specimens fell within the range of pH 6.6 to pH 7.1, although the limits for the whole group were pH 6.0 to pH 7.3.

A number of readings were made on saliva from the same persons at various times to determine whether the reaction was constant in any one individual and if not whether any regular variation occurred (Table IV).

TABLE IV.—VARIATIONS IN pH OF SALIVA IN THE SAME INDIVIDUAL

Name	Period of observation	pH												Total obs.	
		6.0	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1		
Number of observations															
H.	2 months	2	1	...	1	...	2	6	2	1	4	...	...	...	19
Br.	2 days	..	..	..	..	..	..	..	1	..	1	..	..	..	2
Ko.	2 days	..	..	..	..	..	..	..	1	..	1	..	..	..	2
Sch.	1 day	..	..	..	..	..	..	..	..	1	1	..	..	..	2
B.	3 weeks	..	2	..	..	1	..	1	1	..	1	1	2	..	11
D.	1 week	..	..	..	1	..	..	..	..	..	1	..	..	..	2
N.	5 days	..	..	..	..	..	..	..	..	1	..	3	..	1	5
M.	5 days	..	..	..	..	..	..	1	..	1	2	..	1	..	5
Bl.	1 day	..	..	2	1	..	..	..	..	1	..	1	..	..	5

It was found that the variation in the individual covered practically the entire range of the normal reaction, although many of the repeated observations were made at the same time of day and under the same conditions. In a few cases several observations were made during the course of the day to see if there was any regular diurnal variation (Table V).

TABLE V.—DIURNAL VARIATION IN pH OF THE SALIVA

Name	Time	pH	Name	Time	pH
H.	9.15 A. M.	6.6	B.	9.00 A. M.	7.0
	11.45 A. M.	6.6		11.00 A. M.	7.3
	4.15 P. M.	6.6		4.00 P. M.	6.7
	7.30 P. M.	6.3		7.00 P. M.	6.9
In.	9.00 A. M.	6.6	Bl.	9.00 A. M.	6.2
	11.00 A. M.	6.6		1.00 P. M.	6.3
	4.00 P. M.	6.8		2.00 P. M.	7.0
	7.00 P. M.	6.6		3.00 P. M.	6.2
				5.00 P. M.	6.8

A few tests were made to determine the effect of food on the reaction, by examining the saliva immediately before and after meals (Table VI).

TABLE VI.—REACTION OF SALIVA BEFORE AND AFTER MEALS

Name	pH before meal	pH after meal	Name	pH before meal	pH after meal
S.	6.5	6.2	Ma.	6.4	7.3
H.	6.0	6.0	B.	6.5	6.6
M.	6.3	6.3	Bl.	6.2	7.0

No striking changes were noted. Smoking failed to alter the reaction.

Determinations were made to discover any possible alteration in the pH of the saliva following cleaning the mouth and irrigating with the usual gargles used in medical practice (Table VII).

TABLE VII.—EFFECT ON THE pH OF SALIVA OF IRRIGATION OF MOUTH

Name	Procedure	pH before irrigation	pH after irrigation
B.	Mouth washed with 500 c. c. distilled water.	6.9	6.9
L.	Mouth washed with 250 c. c. salt solution followed by 500 c. c. distilled water.	6.4	6.3
C.	Mouth washed with 1000 c. c. distilled water.	6.9	6.9
H.	Mouth washed with 1-1000 potassium permanganate.	6.1	(30 min.) 6.3
B.	Mouth washed with 1-1000 potassium permanganate.	6.6	" 6.6
I.	Mouth washed with 1-1000 potassium permanganate.	6.6	" 6.6
E.	Mouth washed with 1-1000 potassium permanganate.	6.6	" 6.7
H.	Mouth washed with potassium chloride mouth wash.	6.5	(Immediately) 6.7 (30 min.) 6.5
B.	Mouth washed with potassium chloride mouth wash.	6.6	" 6.9 " 6.7
I.	Mouth washed with potassium chloride mouth wash.	6.6	" 6.9 " 6.6
H.	Dobell's solution.....	6.5	" 8.3+ " 6.9
B.	" "	6.6	" 8.3+ " 6.7
I.	" "	6.6	" 8.3+ " 6.6

Washing with distilled water led to no change in reaction of the saliva, and gargling with Dobell's solution, potassium chloride 25 per cent, and potassium permanganate 1-10000 caused only brief alterations which were no longer striking after 30 minutes.

The effect of internal administration of acid and alkali was tested as follows: A normal man received 10 gms. of sodium bicarbonate twice daily until the urine became strongly alkaline. The saliva was tested at various times, care being taken not to collect a specimen until at least two hours after the alkali had been ingested. A similar experiment was performed with hydrochloric acid (Table VIII).

TABLE VIII.—EFFECT OF ACID AND ALKALI ON THE pH OF SALIVA

Name	Date	pH of saliva	Remarks
M.	XII, 2, 19-11 A. M.	6.9	Urine acid. Sodium bicarbonate grams 10 b. d.
	XII, 4, 19-4 P. M.	6.8	
	XII, 5, 19- 4 P. M.	6.8	
N.	XII, 5, 19- 2 P. M.	6.6	Urine alkaline.
	XII, 5, 19- 6 P. M.	6.6	
	XII, 7, 19- 6 P. M.	7.1	
	XII, 2, 19-11 A. M.	7.3	
XII, 4, 19-4 P. M.	XII, 4, 19-4 P. M.	7.1	Dilute HCl 30 drops t. i. d.
	XII, 5, 19- 4 P. M.	6.9	
	XII, 6, 19- 2 P. M.	7.1	
	XII, 6, 19- 6 P. M.	7.1	

The change in the reaction of the urine was not paralleled by any alterations in the salivary reaction.

## REACTION OF THE SALIVA IN DISEASE

Forty-eight observations were made on seventeen individuals suffering from various diseases (Table IX). The reaction

TABLE IX.—REACTION OF SALIVA IN DISEASE

Name	Diagnosis	Date	pH of saliva	Remarks
Br.	Typhoid fever.....	XI, 9, 19 XI, 10, 19	7.0 6.8	Febrile. "
K.	Typhoid fever.....	XI, 9, 19 XI, 10, 19	7.1 6.8	"
C.	Typhoid fever.....	XI, 9, 19 XI, 10, 19	6.9 8.7	Afebrile. "
S.	Broncho-pneumonia.	XI, 7, 19	7.3	Temperature 101° F.
A.	Pernicious anæmia.	XI, 24, 19 XI, 25, 19 XI, 30, 19	6.0 6.0 6.3	
B.	Pernicious anæmia.	XI, 24, 19 XI, 25, 19	6.1 6.1	
T.	Syphilis of larynx...	XI, 8, 19 XI, 9, 19 XI, 10, 19	7.1 6.9 6.9	Scarring of pharynx.
Au.	Chronic nephritis (advanced.)	XI, 24, 19 XI, 25, 19 XI, 26, 19 XI, 27, 19 XI, 28, 19 XI, 29, 19 XI, 30, 19	7.5 7.5 7.5 7.3 7.3 7.3 7.5	Mouth and throat not remarkable. Not getting alkali. Urine acid.
P.	Chronic nephritis...	XII, 1, 19	7.5	
F.	Chronic nephritis...	XII, 1, 19	6.5	
A.	Chronic nephritis...	XII, 1, 19	6.0	On alkali therapy. Urine alkaline.
C.	Diabetes.....	XI, 28, 19 XI, 29, 19 XI, 30, 19 XI, 2, 19 XI, 5, 19 XI, 6, 19 XI, 7, 19	6.2 6.2 6.0 6.5 6.9 6.0 6.9	Acidosis. Blood CO <sub>2</sub> 25 vols per cent. No alkali by mouth. Intravenous alkali. Blood CO <sub>2</sub> 35 vols per cent. Intravenous alkali. Blood CO <sub>2</sub> 50 vols per cent.
D.	Acute stomatitis....	XI, 7, 19	7.0	Blood CO <sub>2</sub> 75 vols per cent.
K.	Acute tonsillitis (streptococcus).	XI, 8, 19 XI, 10, 19	6.2 6.8	Throat acutely inflamed. Throat clear.
W.	Acute tonsillitis (streptococcus).	XI, 14, 19 XI, 15, 19 XI, 17, 19 XI, 18, 19 XI, 19, 19 XI, 20, 19	7.1 6.9 7.1 7.0 7.8 6.9	Throat acutely inflamed. " " " Throat clear. " " " " " "
H.	Acute tonsillitis (streptococcus).	XI, 17, 19 XI, 18, 19 XI, 19, 19 XI, 20, 19	7.1 6.9 6.9 6.9	Throat acutely inflamed. Throat clear.
G.	Acute tonsillitis (streptococcus).	XI, 18, 19 XI, 19, 19 XI, 20, 19	5.8 6.5 6.7	Throat acutely inflamed. Throat clear.

of the salivas fell within the limits found for normals (pH 6.0 to pH 7.3) except in two cases, Au. and P. Three patients with typhoid fever showed a normal salivary reaction. In two instances of pernicious anæmia the reaction was at the lower level of normal on several occasions. Two cases of chronic nephritis had salivas which were distinctly more alkaline than any of the normals, but two other cases of nephritis gave high readings although one of them (A.) had an alkaline urine at the time. A series of five cases of acute streptococcus tonsillitis yielded variable readings within normal limits except for a single observation of 5.8. A diabetic with marked acidosis gave a reading of 6.2. A subsequent reading of 6.0 was obtained at a time when the acidosis had almost cleared up, although the reaction the day before had been 6.9.

## SUMMARY

Study of freshly expectorated saliva from normal people shows that the reaction tested by the colorimetric comparison method may vary within considerable limits—6.0 to 7.3—although 80 per cent of the specimens fell within the range of 6.6 to 7.1. The reaction varied in different individuals and in the same individual at various times apparently without any definite or constant relation to the time of day or to the ingestion of food or fluid. It was temporarily altered by mouth-washes such as Dobell's solution, but only for a short time (30 minutes). Internal administration of acid and alkali did not seem to influence the reaction of the saliva in any definite manner. Observations on a group of patients suffering from a variety of diseases showed no constant relation between the reaction of the saliva and any particular disease, although the variations covered a slightly wider range (pH 5.8 to pH 7.5) than was found in the case of the normal group.

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## PYELITIS ET URETERITIS ET CYSTITIS CYSTICA

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Cystic disease of the renal pelvis and ureter was first recognized by Morgagni, who, in *De Sedibus et Causis Morborum* described the autopsy findings in the bodies of two aged men. His Case IX, in Chapter IV, Section 1, was that of a man 60 years old, indigent, who died suddenly. There were found "hydatids in the substance of the kidneys and ureters, retention of urine from an enlarged prostate and serous infarction of the left thigh and knee. The interior structure of both kidneys contained some small cells full of fluid, one of which showed partly on the surface. Each pelvis was two digits in diameter, both ureters were dilated, the left more so than the right, the left elongated in consequence of flexures. On feeling the ureter there was a sensation of calculi in some portions. Slitting open the ureters disclosed hydatid cysts, some round, others oval, projecting from the inner coat into the canal of the ureter. The round cysts were of the size of small grapes, the oval double the length of the former. The coats of the ureter were thick, the inner uniformly reddened. The ureters opened into the bladder by orifices more oblong than normal. The bladder was distended with urine." In the section on gonorrhœa and syphilis, Case IV is that of a decrepit old man with lues, gonorrhœa and paresis. "The kidneys were small and uneven and the ureters dilated and with the inner surface reddened. In about the middle of the right ureter the inner coat protuberated and doubled itself. Both ureters were filled with mucus and from the middle upwards showed spherical drops of various sizes which could not be wiped away with a sponge. By compressing them they were reduced to a kind of viscid matter tinged with a very faint color of tobacco." The bladder was thickened and trabeculated and there was much pus in the urine.

Until 60 years later no new cases came to light. Johnson in 1816 reported the case of a female who after pregnancy had twice suffered with retention of urine. At autopsy one of the kidneys was found reduced to a shell by hydronephrosis and the ureter was dilated to the size of the iliac artery. The internal surface of the pelvis was highly vascular and studded with mammillary or papillary bodies varying in size from a pinhead to a pea. The cysts did not have the appearance of hydatids, nor were they strictly regarded as due to animal parasites.

These early observers have given us gross anatomical descriptions of a cystic condition of the lining of the pelvis and ureter and associated with it evidences of chronic inflammation in the kidney and ureter. The frequent occurrence of hydatid cysts in the kidney and other organs in Morgagni's experience naturally led him to consider the cysts in the ureter as probably hydatid. From his description of the kidneys the present-

day pathologist would gather that the kidneys were probably of the small arteriosclerotic variety with many retention cysts. His cases were both in aged men. The importance of age in the development of the condition will be discussed later.

Litten, in 1876, made a careful study of a case and introduced the term "ureteritis chronica cystica polyposa." His patient was a man, aged 75 years, with small, shrunken kidneys and the right ureter dilated and studded with cysts. There was a calculus in the right ureter with hydronephrosis. Microscopically, the walls of the ureter were thin and highly vascularized. The cysts contained many free nuclei and masses resembling giant cells with irregularly distributed nuclei-like bodies.

Following Litten's contribution, over 50 cases of ureteritis cystica have gradually accumulated, the greater percentage from the experience of European pathologists, particularly the French and German, but the latter have given the most complete descriptions and have attempted to explain the pathogenesis of the condition. Virchow, Rokitansky and Chiari were acquainted with it, but accorded it scant attention in their works on pathology. Rayer in his Atlas illustrated two beautiful cases under the caption of *éruptions vésiculeuses*. In the latter part of the 19th century there was wider recognition of the disease, and the English observers Eve, Silcock, Sutton, Voelcker and Clark described cases, while Lubarsch, Fränkel, Markwald, Stoerck and others among the Germans, and Albaran, Tuffier, Cruveilhier, Paul Barth, Lancereaux and others of the French writers recorded their experience with the condition. Not until 1902 does it occur in American literature when Harris studied three cases from the Johns Hopkins pathological series. All three were in aged persons, one a woman. Stow, in 1907, added a fourth case and Hibbs, in 1919, contributed a fifth. Recently the writer in doing routine autopsies at the Peter Bent Brigham Hospital encountered three cases in as many weeks and a detailed study of them forms the basis of this paper.

### CASE I

Male, age 83 years, hospital number 21394. Entered the hospital July 24, 1919, in uremic coma. His immediate family history is interesting in that eight out of ten members died in their sixth to eighth decades. The past history is negative except that eight years previously he had been operated upon for prostatic trouble. Since then there had been constant slight trouble passing urine. One week before entrance he felt generally indisposed and soon developed symptoms of uremia. Twenty-four hours before admission acute retention occurred with spasm and twitching of face and arm muscles. There were marked signs of œdema of the lungs and a systolic murmur was heard all over the praecordium. An inlying catheter was inserted into his blad-

der. The urine examination showed an alkaline reaction, sp. gr. 1008 to 1011, a large trace of albumin; the sediment contained a few pus cells and triple phosphate crystals, but no epithelium. Phenolsulphonphthalein output 0, urine output in two hours 12 c. c. The temperature ranged from 100° to 102°, respirations 30 to 40 per minute, pulse 95 to 120 per minute. His condition rapidly became worse and he died about 36 hours after entrance.

#### AUTOPSY DIAGNOSES

**Gross.**—Arteriosclerotic contracted kidneys. Double ureter (left). Hydronephrosis. Right and left ventricular hypertrophy. Pyelitis, ureteritis and cystitis cystica. Healed apical tuberculosi (left). Ruptured abdominal aneurism with extravasation of blood into the retroperitoneal tissues. Tuberculous ulcers of ileum. Chronic fibrous myocarditis. Atrophy of testicle (right). Generalized arteriosclerosis. Prostatic hypertrophy (median lobe).

**Body** is that of a well-developed, rather obese, aged man.

**Primary incision** shows about 3 cm. of normal yellow fat. The pectoral and recti muscles are uniformly paler than normal.

**Peritoneal cavity** contains about 100 c. c. of clear yellow fluid. The omentum, which is heavily laden with fat, is adherent to the sigmoid flexure. The liver extends to within 3 cm. of the lower right costal border and 1 cm. below the xiphoid. Just below the attachment of the root of the mesentery in the midline is an irregular retroperitoneal tumor, about 6 cm. wide, which bulges appreciably into the peritoneal cavity. The mesentery contains much fat and the lymph nodes are small.

**Retropertitoneal Space.**—There is a massive recent extravasation of blood into the retroperitoneal tissues, originating from a ruptured sacculated aneurism of the abdominal aorta about 5 cm. above the bifurcation. Blood has escaped on both sides and while confined strictly to the retroperitoneal region has infiltrated almost the entire right side posteriorly, extending from above and enveloping the right kidney and the tissues inferior to it including the ureter as far as the ureteral entrance in the vesical musculature. On the left side the extravasation extends from the upper level of the aneurismal tumor to the sigmoid flexure. All of the escaped blood is in the form of dark red, gelatinous clot.

**Pleural Cavities.**—The left lung is collapsed. The cavity contains about 150 c. c. of clear, straw-colored fluid. The apex is adherent to the pleura by tough, fibrous bands. There are several fibrous adhesions between the right lower lobe and the diaphragm. In the right side 50 c. c. of clear fluid are present.

**Pericardial cavity** contains about 20 c. c. of clear fluid. There are two polygonal plaques, 8 mm. wide, of thickening of the parietal pericardium overlying the anterior portion of the right auricle.

**Heart.**—Weight 490 gm. It is symmetrically enlarged. The left ventricle is markedly hypertrophied. A considerable amount of yellow fat lies along the coronary sulci and largely covers the intervening spaces. The right auricle is moderately dilated. The tricuspid valve is normal. On the free border of the anterior cusp of the mitral valve is an irregular, pale red nodule, 1 mm. at the base and 2 mm. in height. There is no demonstrable insufficiency. The cusps of the aortic valve are diffusely thickened with calcareous plaques on their facing surfaces. There is good approximation, however. The endocardium otherwise is smooth and pale. The coronary vessels are irregularly thickened, atherosomatous change being most marked, with also a considerable loss of elasticity. The myocardium of the left ventricle shows several areas of fibrosis, the central portion being most affected, and narrow, pale, opaque, white lines leading outward from it in an irregularly radiating manner for 2 to 3 mm.

**Lungs.**—The right lung is emphysematous. The left lung is of similar appearance except that the apex presents a puckered,

thickened area 2 cm. wide, which on section cuts with difficulty and has the appearance of a scar.

**Spleen.**—Weight 130 gm. Acute splenic tumor.

**Gastrointestinal Tract.**—The esophagus, stomach, duodenum and jejunum are normal. In the ileum are two ulcers, each about 2 cm. wide, at the site of Peyer's patches, one 4 cm. and the other 10 cm. from the ileocecal valve. Viewed from the peritoneal surface, the base of each ulcer is greenish-black and surrounded by a zone of petechial hemorrhages. In the lumen these lesions have a crater about 2 mm. deep, bordered by an indurated ring of injected mucosa, but there is no undermining apparent. The base is grayish-green and is covered by thin slime such as is present elsewhere in the ileum. The large intestine shows no lesion.

**Liver.**—Weight 1880 gm. Its surface is smooth and slightly paler than normal. The cut surface shows the lobules fairly well delineated by pale red lines with the central portions yellowish-brown.

**Gall-bladder** is distended with greenish-black mucilaginous bile. The mucosa is normal. The ducts are patent.

**Kidneys.**—Weight of right 110 gm., left 160 gm. The right kidney is much smaller than the left. Both are embedded in much indurated perirenal fat. Two ureters, both of the consistence of a bronchus, lead from the left kidney to unite 4 cm. above the bladder where the lumen becomes narrowed and the consistence normal. The right kidney has a single ureter which is of similar external appearance to those of the left, but is surrounded by blood-clot from its having been enveloped in the massive retroperitoneal hemorrhage from the ruptured aorta.

The right kidney is atrophic and has an irregular, coarsely granular surface from which the thickened capsule strips with some difficulty. The exposed surface is dull red and granular with several cortical cysts .2 to 1 cm. in diameter, projecting slightly above the surface, and containing a greenish mucoid secretion. The organ cuts with difficulty, owing to the great amount of fibrous tissue throughout. The cortex is pale red and thin, in many places being only 1 mm. in thickness. The glomeruli are much diminished in number and those to be seen are just barely visible. The pyramids show much distortion, with pale white opaque lines traversing them in various directions. The pelvic fat is much increased. The pelvis presents many pale, semi-translucent, bead-like projections 1 to 3 mm. wide, containing clear, thin fluid, usually closely arranged and found lining the calices, particularly those of the upper pole. Some of these are surrounded by red, hemorrhagic tissue, which continues to the ureteral orifice. The pelvis is not dilated, but the ureter is enlarged in its entire length by the presence of innumerable pale, cystic bodies 1 to 3 mm. in width, containing clear, watery fluid and which almost occlude the lumen. The ureter is literally studded with these bodies, though they become smaller and fewer as it traverses the bladder wall. A medium-sized probe can be passed into the ureter with difficulty and the passage of urine must have taken place by the process of seepage around the occluding cysts.

The left kidney, although larger than the right, shows no gross evidence of hydronephrosis. The surface markings are similar to those of the right kidney. The cortex is thin and scarred. The pelvic fat completely fills the pelvis and is closely approximated to the pyramids. The lining of the pelvis presents the same studded appearance as in the opposite kidney only to a more marked degree, the calices frequently being distended by the many cysts present. From the left kidney two ureters are given off, one from each pole. They are both enlarged and, until they become united about 4 cm. above the bladder, have an interior appearance like that of the right ureter.

There are none of these growths visible to the naked eye below the point of union of the two left ureters; and the common tube formed has a normal lumen, though slightly thickened walls.

Escape of urine from the left kidney must, too, have been by seepage through the strata of obstructing cysts.

The bladder is large and flaccid. The walls are moderately hypertrophied, the mucosa trabeculated. The posterior portion of the floor is speckled with round, miliary-sized, pale white areas, many of which have a central, pale, cystic eminence not unlike that of the smaller bodies observed in the ureters. The trigone is reddened. The ureteral orifices are not swollen and the passage of a probe is easy. The prostate seems to be present in its entirety and there is a moderate middle lobe hypertrophy. The prostatic urethra appears normal.

**Testes.**—The left is of normal size and "strings out" in a normal manner. The right testis is small, the tunica thickened, the seminiferous tubules being almost entirely replaced by connective tissue.

**Adrenals** are normal.

**Aorta.**—The ascending portion of the arch, although not dilated, shows several irregular thinned out areas from .3 to 2 cm. wide, to which pale red, elastic thrombi are attached. The edges are raised and appear to be composed of atheromatous deposit. Continuing along the aorta until the level of the renal arteries is reached, the same condition is seen with much roughening from projecting, jagged yellow plaques and diffuse intimal thickening with calcification.

About 2 cm. below the opening of the superior mesenteric artery on the left posterior wall is a sacculated aneurism about 4 cm. in depth. It is outlined by ragged, hard and yellowish, slightly raised, atheromatous-looking tissue and the crater is filled partially with dark red recent thrombi and older gray elastic mural thrombi. A perforation exists about 1 cm. wide in the central portion and there has been considerable extravasation of blood, with dissection between the media and adventitia above to as far as the mesenteric artery and below to within 4 cm. of the iliac bifurcation. The surrounding connective and fatty tissue is infiltrated with blood, the entire mass being firm and elastic. The iliac arteries are tortuous and irregularly thickened with atheromatous and calcified plaques in their walls. The mesenteric, renal and hepatic arteries are of similar appearance and mural thrombi are present in some of the smaller branches of the mesenteric artery.

#### MICROSCOPICAL EXAMINATION

**Heart.**—The sections show a considerable degree of coronary sclerosis and areas of fibroplasia in the interstices with atrophy of muscle fibers in these areas. There is rather marked brown pigmentation of the myocardium.

**Lungs.**—Negative.

**Spleen.**—Acute splenitis with marked elastoid degeneration of the arterioles.

**Liver.**—There are numerous necroses irregularly distributed as regards their position in the lobule, and usually involving two to five liver cells. Others are larger and in the peripheral zone. There is a moderate degree of portal sclerosis with infiltration by plasma and lymphoid cells. The branches of the hepatic artery show marked hyalin changes in the media.

**Kidneys.**—Both show a marked grade of chronic vascular nephritis. The vascular lesions consist of an advanced degree of intimal thickening of the renal arteries with hyalin changes in their walls, sclerosis of the arterioles rectæ, hyalinosis of the afferent arterioles of the glomeruli and all stages of similar change in the glomerular capillaries. Most of the glomeruli are completely fibrosed; the surrounding tubules are replaced by fibrous tissue in which are many lymphoid and plasma cells. There is atrophy and dilatation of other groups of convoluted tubules. In the medulla there is marked infiltration with mononuclear cells and polymorphonuclear leucocytes, many of the latter filling collecting tubules. Hyalin casts are present in most of the tubules in the

pyramidal zone. A moderate degree of hydronephrosis is indicated by the dilatation of the collecting tubules and accumulation therein of albuminous fluid.

**Ileum.**—A section of the ulcer shows it to extend nearly to the muscularis, being rather sharply outlined there with slight undermining of the mucosa at one edge. Typical tubercles are present in the submucosa of the adjacent non-ulcerated portions and in the floor of the ulcer. Miliary tubercles are present in between the muscle fibers of the circular layer. Many vessels show thrombosis with organization and canalization.

**Adrenals.**—The arteries show much thickening of the intima and hyalinosis of the media. The cortical cells have a high lipid content; certain areas show degeneration of cells and proliferation of fibroblasts in the intercellular spaces with migration of a few wandering cells.

**Ureters.**—Sections from the very cystic portions of the ureters at different levels show the same general picture. The projecting cysts are lined with low cuboidal epithelium in two or three layers along the base, but only a thinned single layer in the greater part of its inside circumference. The contents are a more or less homogeneous eosin-staining material which has retracted somewhat from the walls. In it are numerous large, round or elliptical bodies with dark pyknotic inclusions which suggest nuclear fragments. Fat droplets are present in some. Along the periphery are many degenerated epithelial cells and desquamated normal-looking cells of the lining. The granular nature of portions of the cystic contents with the degenerated cells along the border make it appear probable that much of the material in the cysts has that origin. A thin connective-tissue envelop surrounds the cysts, but no definite epithelial elements can be made out. The origin of these growths seems very likely from "nests" of epithelial cells of the type of the ureteral lining, as these can be seen in the less involved parts and in the bladder, lying in the mucosa. These "nests" of cells are surrounded by a connective-tissue stroma rich in blood-vessels and in which lymphoid cells are often present in numbers. There is proliferation of these cells followed by degeneration and cyst formation with swelling toward the surface. All these stages are found. The smooth muscle of the ureter is atrophied and invaded by considerable connective tissue.

#### CASE II

Male, age 74 years, hospital number 21829. A Civil war veteran who entered the hospital complaining of shortness of breath and swelling of the abdomen and limbs. His past history was irrelevant, except that for the past 15 years he had had frequent nocturia. His present illness had begun about two years previously with shortness of breath on exertion. Other symptoms of decompensation of the heart had occurred and recently anasarca had gradually developed. Upon physical examination he was very dyspneic and cyanotic, with respirations Cheyne-Stokes in character. There was general anasarca. The heart was in auricular fibrillation. The peripheral arteries were markedly thickened. Blood-pressure 188 systolic, 116 diastolic.

Under the Karel diet and digitalis he lost 3.7 kilos in weight. Two thousand cubic centimeters of fluid were removed from the right chest. He became steadily weaker. Venesection was done, 300 c.c. of blood being removed. On the fourth day he died. Clinical pathology: Urine on two examinations, amber, acid, sp. gr. 1018 to 1020, albumin a trace. Blood examination including the Wassermann was negative.

#### AUTOPSY DIAGNOSES

**Gross.**—Chronic myocarditis. Acute hemorrhagic necrosis of pancreas. Double hydrothorax. Hydropericardium. Ascites. Edema of extremities. Left and right ventricular hypertrophy.

Healed abscesses of left kidney. Cystic cystitis. Double hydrocele. Arteriosclerosis.

*Body* is that of an aged white man, rather obese. There is marked pitting œdema of the lower extremities.

*Primary incision* shows panniculus about 3 cm. in thickness. There is moderate œdema of the chest and abdominal walls.

*Peritoneal cavity* contains about 200 c.c. of yellowish fluid tinged with blood. There are no adhesions. The liver extends 4 cm. below the right costal border and 3 cm. below the ensiform. The mesenteric lymph nodes are considerably enlarged, due to œdema.

*Pleural Cavities*.—The left contains 700 c.c. of straw-colored fluid; the right, 900 c.c. of similar fluid.

*Pericardial cavity* contains 120 c.c. of yellow fluid. There is no displacement of the heart.

Heart weighs 700 gm. Measures *in situ* 17 x 11.5 cm. The left ventricle is greatly hypertrophied, the right ventricle moderately hypertrophied. The right auricle is dilated. The tricuspid, pulmonic and mitral valves are normal. The aortic valve leaflets show no distortion although the mural halves of the cusps are composed chiefly of a gritty, calcareous material. The endocardium as a whole is of the normal red color. Sections through the left ventricle in different places show the myocardium uniformly of the normal red color, firm, and without evidence of fibrosis or fatty infiltration. The coronary arteries are considerably thickened. The lumen, as far as it can be traced, is of normal width. Atheromatous plaques are numerous along the course of the coronary arteries and in places there is some calcification in these deposits.

*Lungs*.—Weight of right lung 600 gm., left 540 gm. Both are moderately emphysematous, and the posterior portions are full of œdematosus fluid.

*Spleen*.—Weight 210 gm. It is enlarged, purplish-red in color. The surface is tense. On section the pulp is dark red and firm.

*Gastrointestinal Tract*.—The mucosa of the oesophagus, stomach and duodenum is dull red, especially along the tips of the folds. The contents are thin fluid in nature. The rest of the intestinal tract shows no lesion.

*Pancreas*.—There is a considerable amount of congestion in the more central portions and along its entire length. The lobules are prominent, although there is considerable œdema throughout the organ.

*Liver*.—Weight 1710 gm. Its surface is deep, reddish-brown and rather tense. Capsule in places is rather opaque and thickened. Upon section there is throughout a somewhat nutmeg appearance. The central veins appear congested. In one place, about 5 mm. below the capsule in the anterior surface of the right lobe, is a round, white area about 3 mm. in width which appears calcified.

*Gall-bladder* shows considerable fluid beneath the serosa. It is swollen and œdematosus and contains about 30 c.c. of a thin, black bile. The ducts are patent.

*Kidneys*.—Weight of right 250 gm., left 240 gm. The capsule strips easily from a very slightly granular, dull red surface. The cortex varies in width from 4 to 8 mm. The surface as a whole is considerably congested and red in appearance. The glomeruli are very prominent as dull red dots projecting above the cut surface. The pyramids have dull red striations alternating with slightly brighter red lines. The pelvis shows no lesions, the lining being smooth and white. The left kidney shows here and there in several of the pyramids about 15 mm. above the tip, round, white, encapsulated lesions about 3 mm. in width. They cut with considerable resistance. A frozen section of one of these shows it to consist almost entirely of vascular fibrous tissue. These lesions probably represent healed abscesses.

*Adrenals* are normal.

*Ureters* are opened at different levels and appear normal.

*Bladder* contains about 100 c.c. of turbid urine. The mucosa about the ureteral orifices and in the trigone present numerous small vesicles 1 to 1.5 mm. in width and containing a clear fluid. These cystic bodies are more numerous in the trigone than elsewhere and the trigone itself is somewhat injected.

*Genitalia*.—There is a double hydrocele. The testes string out normally.

*Aorta* is of normal elasticity throughout its entire length although there are numerous large atheromatous plaques, especially about the opening of the intercostal arteries. To some of these plaques flecks of fibrin are attached. The iliac arteries, 4 cm. below the bifurcation in the posterior walls, are much thickened. There is a good deal of puckering of the intima about these areas.

*Heart*.—A section through the left ventricle wall shows the muscle fibers hypertrophied to a marked degree. There is moderate interstitial œdema and the capillaries as a whole are congested. The muscle of the walls of the arteries is hypertrophied, but the lumen is not narrowed and there is but very slight evidence of fibrous myocarditis.

*Lung*.—The alveolar capillaries are moderately congested and in the alveoli is considerable œdematosus fluid. Hemosiderin-laden phagocytes are numerous in many alveoli.

*Spleen* is typical of chronic passive congestion.

*Liver*.—There is marked central zone congestion with pressure atrophy of the liver columns of the congested areas. Endothelial leucocytes are numerous in many of the portal spaces. The capsule is diffusely thickened and in one place is a patch of pericholangitis in which are many mononuclear cells and fibroblasts.

*Pancreas*.—The section shows a very marked degree of acute hemorrhagic necrosis superimposed upon an old chronic interstitial pancreatitis. The lobules are still defined by fibrous tissue in which massive hemorrhage has occurred. The acini in most of the lobules show acute degenerative changes. There is a diffuse increase in connective tissue throughout many lobules. Fat necrosis has occurred in and immediately about the areas of hemorrhage. A feature of the section is the entire lack of acute inflammatory exudate about the necrotic areas, only a few lymphoid cells being seen beneath the capsule in places. The islands of Langerhans are destroyed, except a few in the peripheral, more normal-appearing portions of a few lobules. The arteries are markedly sclerosed and although no actual rupture can be made out, a few show R. B. C. infiltration between media and adventitia. The picture is that of a "pancreatic apoplexy" or Chiari's "acute hemorrhagic pancreatic necrosis." The pancreatic duct was not investigated thoroughly enough to rule out obstruction to it.

*Aorta*.—A section of the aorta is taken through a typical atheromatous plaque of large proportions. Fat crystals are present in great numbers in the thickened intima. The elastica is frayed out at the margins. About the vasa vasorum mononuclear cells have infiltrated in numbers.

*Kidney*.—There is marked congestion and œdema of both cortex and medulla, with considerable albuminous granular material in the glomerular spaces. The glomeruli as a whole deviate but slightly from the normal, an increased number of nuclei in the tuft, endothelial cells and occasionally lobulation of the tuft being seen. Beneath the capsule, which is somewhat thickened, are several foci of lymphocytes and similar foci are seen scattered through the cortex, and in the vicinity of these interstitial fibroplasia has occurred. The afferent arteries of the glomeruli show quite uniformly hyalin thickening of their walls and the larger arteries a marked degree of sclerosis. Hyalin casts are present in many collecting tubules. The tubules in the medulla show moderate to fairly marked changes of hydronephrosis. The pelvic epithelium has largely been destroyed and replaced by a

vascular granulation tissue rich in plasma, lymphoid and eosinophilic cells.

**Ureters.**—The lesions may be summed up as a marked chronic inflammation of the mucosa with cell "nests" and crypt formation, atrophy and fibrosis of the circular and longitudinal muscle bundles. All levels are involved in these changes. In the upper half the most marked changes have occurred. The epithelial lining has largely been destroyed, leaving exposed a very vascular connective tissue in which are large numbers of mononuclear phagocytes, small lymphocytes, plasma cells and a few polymorphonuclear leucocytes. A few short, thick bacilli are visible with Goodpasture's acid-fuchsin stain. Embedded in this inflammatory tissue are numerous "nests" of epithelial cells, some directly beneath the surface, others connected with it by a very narrow strand of epithelial cells. Most of these "nests," however, have lost all connection with the lumen of the ureter and lie isolated (as serial sections show) in the tunica propria. In no case has herniation through or growth into the muscularis occurred. These "nests" vary much in size. Many are of from 10 to 30 cells, others are slightly larger and show degeneration in the center with consequent lumen formation. The individual cells are polyhedral or more or less columnar, varying with the amount of degeneration in the center. Several sections show large cysts bulging into the lumen of the ureter from all sides. These are lined with a transitional to low columnar epithelium, and contain a basophilic or neutrophilic material, in some cysts homogeneous like colloid, in others granular and containing desquamated epithelium much like the picture of a follicle of an old hypertrophied prostate.

The circular and longitudinal muscle fibers are atrophic; many contain large, clear vacuoles about the nucleus. The muscle fasciculi have been invaded by connective tissue in such amount that many contain only a few muscle fibers, the great part having been replaced by fibrous tissue. The arteries show moderate sclerosis.

In the lower half of the ureters the histogenesis of the cystic condition is well brought out. The lining epithelium is still preserved, but excessive infolding of the mucosa has produced deep folds and crypts and many smaller and shallower infoldings. The subepithelial tissue or tunica propria is made up of tissue in which are numerous fibroblasts, wandering tissue cells, lymphocytes and a few polymorphonuclear leucocytes. This inflammatory tissue in many instances is seen to have extended across where the upper edges of the folds meet and cut off groups of epithelial elements from the lumen of the ureter.

These "nests" of cells have no basement membrane nor any of the characteristics of true glands. The same degree of muscular atrophy and fibrosis is seen in the lower half as in the upper half of the ureter.

**Bladder.**—The lining epithelium is still present in a few places in the section, as a fairly well-defined transitional type. It has largely disappeared, however, and been replaced by a very vascular chronic inflammatory tissue in which are large numbers of lymphoid and plasma cells and in one section are two rounded nodular prominences composed almost entirely of lymphoid cells.

The epithelial lining cells show very strikingly the formation of cell "nests." Deep infolding is observed in several places and in others the upper portions have fused owing to the overgrowth of inflammatory tissue and the "nests" have thus been cut off. Some of these contain a lumen due to degeneration in the central portion.

The smooth muscle in the bladder shows moderate hypertrophy and invasion by much connective tissue. The blood-vessels of the muscularis are congested and wandering cells are present in various portions.

Sections from the posterior wall, trigone and prostatic urethra show marked chronic cystitis with numerous small epithelial

"nests" cut off from the surface by the overgrowth of granulation tissue. A few projecting cysts of small size are seen in sections of the posterior border of the trigone. The glands of the prostatic urethra contain much desquamated epithelium and a moderate number of corpora amyacea.

**Testicle.**—There is marked atrophy of the cells of the tubules, although an occasional spermatozoon is seen. The basement membrane of the tubules is markedly thickened and the arteries show advanced sclerosis.

#### MICROSCOPICAL DIAGNOSES

Acute hemorrhagic pancreatic necrosis. Chronic fibrous myocarditis (slight). Cardiac hypertrophy. Chronic passive congestion. Chronic pyelitis. Healed cortical abscesses of kidney. Chronic ureteritis and cystitis cystica. Hydronephrosis (moderate). Chronic perihepatitis. Atrophic orchitis. Generalized arteriosclerosis.

#### CASE III

Male, age 66 years, hospital number 21088. Entered the hospital very drowsy, with swelling of the legs and shortness of breath. Two years previously he had had a prostatectomy following urine retention and nocturia regarding which a note from Dr. George Gilbert Smith says:

"On May 21, 1917, I did a perineal prostatectomy under spinal anaesthesia. A very large, typical adenomatous prostate was removed, also a stone in the bladder. His convalescence, except for an epididymitis, was uneventful. At that time he had a blood-pressure of 200 with cardiac enlargement and a systolic murmur."

"I saw Mr. T. again on July 12, 1918. He was complaining of haematuria. I cystoscoped him and found that bloody urine was coming from the left ureter. His blood-pressure was 240. It seemed to me that his haematuria was due to nephritis."

Otherwise his past history was unimportant. His present illness had begun about six months before with haematuria, which had increased until at entrance he was passing nearly pure blood. His legs had begun to swell four months later but the swelling was somewhat relieved by digitalis. He was dyspneic on exertion and the edema of his extremities increased steadily. Physical examination showed general anasarca, much wasting and an enlarged heart with poorly transmitted sounds. There was a markedly urinous odor to the breath.

Under treatment his heart action improved and most of the edema disappeared. The blood-pressure ranged for many days from 150 to 190 systolic and 90 to 130 diastolic. The blood urea averaged about 45 mg., but reached 74 mg. at one time with only a trace of phenolsulphonphthalein excreted. The urine always showed a large amount of albumin, hyalin and granular casts. After being in the hospital 75 days he developed gangrene of the right foot with absence of pulsation in the popliteal artery of that side. He showed Cheyne-Stokes respirations almost constantly, the temperature rose from 99° to 102° and shortly before death to 107° with signs of pneumonia. He died on the 77th day.

#### AUTOPSY DIAGNOSES

**Gross.**—Chronic myocarditis with cardiac hypertrophy. Bilateral broncho-pneumonia with purulent bronchitis. Thrombosis of right auricular appendage. Bilateral hydrothorax. Sclerosis of the coronary arteries. Senile aortic arteriosclerosis. Bilateral pyonephrosis with marked atrophy of the renal medulla and cortex accompanied by bilateral renal calculi occupying the renal pelvis and extending down into the ureters. Bilateral perinephritis. Pyelitis, ureteritis and cystitis cystica. Chronic fibrous perisplenitis with passive congestion of spleen. Passive congestion of the liver. Cholelithiasis. Petechial gastric haemorrhages. Haemorrhagic colitis. Visceroptosis. Gangrene of the

lower right leg with thrombosis of the anterior tibial artery with possible involvement of the external popliteal.

*Body* is that of a very emaciated male, white adult. The skin is dry and thick. The lower part of the right leg and the right foot present a bright red discoloration, the hue gradually increasing in intensity distally from the calf. This entire distal portion of the right lower extremity is red, slightly boggy and the skin covering it is moist and desquamating. Upon excising the proximal portion of the anterior tibial artery it is found to have been recently thrombosed, the lumen being occluded by a soft red blood-clot for a distance of several centimeters with probably extension into the external popliteal artery. An organized mural thrombus in the anterior tibial artery in the lower tibial region occludes about one-third of the lumen.

*Primary incision* discloses very little subcutaneous fat and markedly atrophic pectoral and abdominal muscles.

*Peritoneal Cavity*.—There are numerous adhesions of the omentum to the sigmoid flexure, to the liver and the right lateral abdominal wall. The parietal peritoneum is elsewhere smooth and glistening. There is marked ptosis of the viscera, but especially of the cæcum, the transverse colon and the sigmoid. The cæcum and the appendix have entirely descended into the pelvic cavity.

*Pleural Cavities*.—The left pleural cavity contains 850 c.c., the right 540 c.c. of reddish fluid.

*Heart*.—Weight 650 gm. It is markedly hypertrophied. The pericardium is smooth and does not show any roughening or adhesions. The myocardium of the left ventricle measures approximately 2 cm. in thickness. It is firm, pale, but does not show any particular increase of connective tissue. The endocardium is smooth with here and there evidence of some fat. There are no valvular lesions and the cardiac chambers are empty aside from a small, fragile, reddish thrombus in the right auricular appendage. The coronary arteries are somewhat sclerosed as is also the proximal portion of the aortic arch.

*Lungs*.—The right lung weighs 545 gm., the left lung 405 gm. The external appearance of both lungs is grayish-white. Both crepitate upon pressure. Upon section, the cut surface is grayish and moist. Upon pressure, frothy fluid escapes from the alveoli and puriform matter runs from the larger bronchioles. In the lower lobes there are areas of firmer consistency, reddened, and standing out in contrast with the surrounding lung tissue. In several places along the periphery of the lung there are areas of firmer consistency which do not crepitate upon pressure and on section show a reddened, moist surface.

*Spleen*.—Weight 170 gm. The external surface of the spleen is covered with numerous small white masses appearing like beads. These are embedded in the capsule. The spleen sections easily and the cut surface is dark red and of firm consistency.

*Gastrointestinal Tract*.—The esophagus is normal. In the fundus region of the stomach there are present groups of petechial hemorrhages. There are probably as many as 20 of these, the individual hemorrhages being about the size of the head of a pin. The duodenum, jejunum and ileum are normal aside from the ptosis. The cæcum lies in the pelvic cavity and is greatly distended with fecal material. The ascending colon is not remarkable, but the transverse colon is markedly posited and contains very hard, scybalous fecal matter. Similar scybalous ball-like masses are found in the descending colon, the sigmoid and the rectum. The external appearance of the colon is dark and congested. The mucosa is markedly reddened, while in four or five places in the mucosa of the transverse colon there are definite hemorrhagic areas about 1 cm. in size.

*Pancreas*.—Normal.

*Liver*.—Weight 1560 gm. It is moderately congested. The gall-bladder contains about 20 c.c. of dark brown bile and four small gall-stones. The gall-ducts are patent.

*Kidneys*.—Each kidney weighs 285 gm. *In situ* they are very irregular in outline, covered and embedded in a great deal of indurated perirenal fat, while in the pelvis of each kidney a hard, rock-like mass can be palpated, apparently directed downward toward the ureter. The ureters also appear to be edematous, enlarged in circumference, soft and boggy to feel. In extricating the kidneys great difficulty is experienced, as they do not shell out of the perirenal fat as usual, but have to be dissected away. In the attempting to remove this it is found that the renal capsule is also so adherent that it strips with difficulty from the surface leaving a red, granular, irregular surface, showing here and there cicatrical contractures and depressions. Separating rough granular areas are portions of cortex, smooth, depressed and fluctuant. Upon sectioning, the kidneys both present a strikingly similar picture. The pelvis of each is occupied by a large, hard, light brown stone securely anchored in place by its ramifications in the renal calices and directed downward into the opening of the ureters. There is very marked œdema of the pelvic fat. The pelvic lining is congested, and there are numerous blotchy haemorrhages beneath. The renal calices are seen to be greatly enlarged, several of them being distended with semifluid puriform material. The overlying medulla and cortex are but a thin sheet. In other places the cortex measures as thick as 5 mm. and is very congested.

*Ureters*.—Both ureters and the distal portion of the pelvis when opened have an inner surface made irregular by the presence of numerous vesicular growths, in size varying from a pin-head to 3 mm. and separated about .5 to 1 cm. from each other. These vesicles are colorless and contain a thin, turbid fluid, which spurts on opening. Many of these bodies are pedunculated and hang downwards in the ureters like minute pears. They diminish in number gradually toward the bladder and about 3 cm. above that organ they are not visible. The remaining mucosa is pale and granular. The ureteral wall as a whole is thicker than normal.

*Bladder* contains about 50 c.c. of turbid urine. The ureteral openings are patent. Scattered irregularly over the mucosa, more especially just outside the trigone, can be seen an occasional projecting cystic body about .5 mm. in width. The bladder mucosa, however, is of normal appearance except for these cysts and slight injection of the trigone.

*Aorta* shows marked senile arteriosclerosis.

#### MICROSCOPICAL EXAMINATION

*Heart*.—The muscle fibers are moderately hypertrophied and many contain hydropic vacuoles. There is a diffuse increase in interstitial connective tissue and beneath the endocardium a few irregular patches show a considerable degree of fibrosis with atrophy of the muscle fibers. The coronary arteries present various grades of sclerosis, many have hyalin changes in their media and one shows early calcium deposition about the hyalinized layer. The capillaries as a whole are congested and there is moderate interstitial œdema.

*Lung*.—There is one section which is not remarkable except for rather marked sclerosis of the branches of the pulmonary artery and the presence of a spicule of bone about 1.5 mm. in width lying next to an interlobular septum in which there is a considerable amount of carbon pigment. Throughout the section large mononuclear cells containing hemosiderin granules are quite numerous in the alveoli.

*Spleen*.—The pulp is markedly congested and contains many large mononuclear phagocytes containing fat vacuoles. The lymphoid tissue has largely disappeared. The arteries of the malpighian corpuscles show pronounced elastoid degeneration.

*Liver* is characteristic of the early reparative stage following the central necroses of chronic passive congestion.

**Kidneys.**—They are remarkable for showing both an extreme grade of arteriosclerotic change and pyelonephritis with cortical abscesses. Most of the glomeruli are completely fibrosed and the afferent arterioles and larger arteries show very marked sclerosis. There has occurred marked atrophy of the cortical tubules with great interstitial fibrosis and infiltration with lymphoid, plasma cells and polymorphonuclear leucocytes. There is marked congestion throughout the organ, but most conspicuously in the medulla. Several small abscesses are present in the boundary zone and in many of the collecting tubules are calcified or hyaline casts. The pelvic epithelium has entirely disappeared and very vascular granulation tissue forms the lining of the pelvis.

**Gastrointestinal Tract. Stomach.**—The mucosa of the fundus shows numerous hemorrhages into the folds from rupture of capillaries. The hemorrhages vary in size, the largest occupying the greater part of two contiguous folds. The lining epithelium is desquamated from over the areas and the mucosa as a whole is very atrophic. There is no cellular reaction about the hemorrhages.

**Duodenum.**—There are a few very small hemorrhages in the submucosa.

**Large Intestine.**—There are many hemorrhages similar to those in the stomach only more extensive, involving the interscissures of several adjoining crypts.

**Pancreas.**—There is a moderate amount of fatty infiltration between the lobules. The parenchyma is normal.

**Ureters.**—Sections from the upper third of each ureter show the lining epithelium in many places replaced by a chronic inflammatory tissue. Many "nests" of cells similar to the lining epithelium are found in the connective tissue of the mucosa. Many of these have undergone cystic degeneration and several project prominently above the surface so as to partially obliterate the lumen. The cysts are lined with a single to triple layer of epithelial cells and covered by a thin, fibrous envelop. The process appears to be due to the marked infolding of the mucosa, the muscle fibers being very atrophic, and connective tissue being increased in amount both in the tunica propria and between the atrophic muscle bundles. The tips of some folds have become closely opposed and granulation tissue has bridged the interspace cutting off "nests" of cells which ordinarily line the deeper portions of the crypts. The arteries show moderate sclerosis.

**Bladder.**—The mucosa has been largely replaced by a vascular granulation tissue, the epithelium being entirely absent in the section except in a few places near the ureter where a few "nests" with cysts appear. The content of the cysts is a more or less homogeneous material, the peripheral portions eosinstaining and the central parts deeply basic. Fat-laden phagocytic cells and nuclear fragments are numerous in the cysts. The smooth muscle shows evidence of previous hypertrophy followed by extensive fibrosis between the fasciculi and individual muscle fibers.

#### MICROSCOPICAL DIAGNOSES

Pyelonephritis with cortical abscesses. Arteriosclerotic nephritis. Chronic fibrous myocarditis. Generalized arteriosclerosis. Coronary sclerosis and calcification. Cardiac hypertrophy. Multiple hemorrhages into mucosa of stomach, duodenum and large intestine. Chronic passive congestion of liver with central necroses. Chronic ureteritis and cystitis cystica. Bone metaplasia in lung.

#### ORIGIN OF CYSTS OF THE URINARY TRACT

The literature regarding pathogenesis is very abundant in hypotheses. This is in a degree due to the finding in one

case of cysts in the kidney, ureter and bladder, in another cysts in the pelvis and ureter, in others only in the bladder in the region of the trigone or prostatic urethra. The similarity of the epithelium lining these organs was apparently not fully appreciated. All the explanations so far offered for the condition may be divided into three main groups: (1) That the cysts are parasitic in nature; (2) that they are derived as retention cysts from pre-existing glands in the pelvic, ureteral or vesical mucosa; and (3) that they originate from the cell "nests" of von Brunn.

The idea that the cysts are due to parasites had supporters for many years, but toward the end of the 19th century was almost entirely discarded, no cases having been proven, although the possibility was not denied. The variety of parasites declared responsible for the cystic condition served to throw legitimate doubt about the whole argument. Morgagni interpreted the cortical cysts in small granular kidneys as hydatid and those of the ureters were also thus considered. In Eve's case psorosperms or pseudonaviculae of the Gregarinidae and in Sutton's case coccidium oviforme were thought to be the causative agents. Pisenti and von Kahlden were also in favor of a protozoan etiology. In Fig. 3 the four cysts to the right contain in the colloid matrix numerous rounded or oval bodies which seem identical with Eve's "psorosperms." They are, however, like no known parasite, being composed of a central mass of pyknotic nuclear substance embedded in material of a fatty or lipoid nature with usually no definite limiting membrane. In the cyst on the left these bodies are present in such numbers that many have fused to form irregular granular masses with nuclear fragments undoubtedly derived from broken down epithelium or leucocytes. Further doubt was thrown upon the possibility of these bodies being parasites by the work of Gilchrist, who showed that degeneration of epithelium gives rise to particles which simulate and have been called psorosperms, organisms of blastomycotic dermatitis and other allied affections.

Virchow and Chiari believed that the cysts were retention cysts from pre-existing glands in the mucosa of the ureter or bladder in which a catarrhal inflammation usually existed and which was regarded as the cause of the blocking of the gland ducts. Litton was of a similar opinion. In the older text-books of histology, mucous glands were usually mentioned as occurring normally in the ureter, particularly in the upper third. Wendt, Hamburger and Egli described gland-like structures in the mucosa; but recent opinion is that normally there are no true glands in the mucosa of the pelvis, ureter or bladder of man. What gland-like formations have been found were apparently due to proliferation of the surface epithelium or excessive infolding of the mucosa. In the region of the prostatic urethra aberrant urethral glands and prostatic follicles were considered by Lubarsch as possible forerunners of macroscopic cysts.

The view finding widest acceptance in recent years is, with various slight modifications, that the cysts are derived from groups of epithelial cells which become isolated from the

lining of the mucosa and lie in the tunica propria. These epithelial groups are known as the cell "nests" of von Brunn, as this investigator gave them the first careful consideration, although Unruh, Egli and Hamburger had previously noted their presence in the ureter and pelvis. Von Brunn working with organs of condemned criminals was unable to demonstrate them in the renal pelvis, but in the ureters and bladder he described grape-like adenoid bodies composed of cells similar to the lining epithelium lying in the tunica propria. These at first were connected with the overlying epithelium and ran vertical to it, later assuming a more parallel position and finally becoming detached to form "nests." He believed, then, that these "nests" were isolated groups of cells derived from invaginations and crypts of surface epithelium which Hamburger and others regarded as mucous glands.

The occurrence of von Brunn's cell "nests" appears to have a definite relationship to the age of the individual. Aschoff states that no "nests" of von Brunn occur in the ureters of the newly born or in early life, and that they are inconstant in adult life. Markwald found ureteritis and cystitis cystica in a newly born, and claims with Aschoff that inflammation is not *first* necessary to originate the "nests" and crypts. In the ureters of eight infants from five days to eighteen months old the writer was unable to find any "nests," sections being taken from ten levels of each ureter. These findings then are in agreement with Aschoff's, and the writer cannot but believe that in Markwald's case the "nests" must have had an inflammatory origin.

However, text-books of histology describe them as found normally in adult ureters. No doubt a few occur in middle life, but it is also true, at least in the writer's experience, that they increase in number with age, being most plentiful after 50. It is a striking fact that ureteritis cystica is a disease chiefly of old age, over 95 per cent of cases occurring after the 50th year, and a large number in the seventh and eighth decades. The figures as to sex are about equally divided.

Stoerck insists there must *first* be inflammation to cause cell "nests" even though all traces of it disappear. He calls attention to the fact that there is nothing analogous to von Brunn's "nests" in other mucous membranes of the body in extra-uterine life. However, the heteroplasia of epithelium lining the gall-bladder is a somewhat similar phenomenon. Saltikow met with three cases of ureteritis cystica and four cases of pyelitis cystica, and in six of these cystitis cystica was present. Of 15 cases of cystitis cystica diagnosed macroscopically four were in patients 30 to 50 years of age and nine occurred between the 60th and 87th years. He was of the opinion that von Brunn's "nests" were associated practically always with inflammation, that they were not normal structures. Herxheimer, also, emphasized the importance of the inflammatory factor. These authors believed that through degeneration of these groups of epithelial cells cut off from the surface the cysts of the pelvis, ureter and bladder arose. Lubarsch attributed their origin to three sources: (1) Mucous crypts; (2) epithelial "nests" of von Brunn; and (3) in the bladder

from abnormally placed urethral glands. In 3000 autopsies he found cysts of the renal pelvis twice, and in the ureter four times, all in patients over 70 years of age.

Certain experimental work is of interest in this connection. Giani in studying tuberculosis in rabbits inserted gelatin capsules into the bladder through a suprapubic cystotomy and found that cell "nests" and cysts were formed at the site of injury. Cysts were also produced by irritation of the mucosa with a Volkman spoon.

Garre, quoted by Buerger, describes "traumatic" epithelial cysts, the "atheromatous" cysts of the Germans, as occurring on the volar aspect of the hand and fingers from pieces of epithelium becoming mechanically displaced in the deeper tissues. Kaufman buried pieces of epithelium of the cock's comb and sutured the edges together, cysts being formed. Sutton has termed such implantation cysts. These traumatically displaced bits of epithelium are in many ways analogous to the cell "nests" in the pelvis, ureter and bladder, where the transformation into cysts is also accomplished.

Some correlation of the various views on the pathogenesis of cystic ureteritis, pyelitis and cystitis is necessary, although modern opinions do not show wide variance. The symptomatology is obscure. Cysts in the pelvis and bladder probably give no symptoms. In a narrow muscular tube like the ureter a moderate number of cysts might conceivably interfere with normal peristalsis. When they are in such numbers as in Case I, they no doubt are able to produce hydronephrosis *per se*, although frequently there has been a history of urinary calculi which might account for the hydronephrosis present. Examination of the urinary sediment has been ... *no* help in diagnosing the lesion.

The writer's three cases were all in old men, two with a history of prostatic trouble and the third with bilateral renal calculi and pyelonephritis. The kidneys of all three showed advanced arteriosclerotic nephritis. There was generalized arteriosclerosis, particularly of the ureteral and vesical arteries. The photomicrographs show plainly the histogenesis of the cysts of the ureter and bladder. The arteries of these organs show much thickening and there are muscular atrophy and very marked fibrous myositis. These lesions possibly produce a degree of atony to account for the subsequent excessive infolding of the mucosa. Hypertrophy of the myoureter occurs after obstruction, to be followed later by the invasion of fibrous tissue. An increase of fibrous tissue throughout the tunica propria takes place, apparently an upgrowth toward the lumen to a considerable extent, and numbers of epithelial "nests" are formed. Many in addition originate through the superimposing of an infection with healing over of tips of folds of mucosa by granulation tissue. Ureteritis cystica in young individuals probably originates from cell "nests" formed in this manner. The inflammatory irritant causes both proliferation and degeneration of epithelium (mitotic figures may be seen in "nests" (Saltikow)), and the degeneration with transudation of fluid forms cysts which increasing in size come to bulge into the

lumen. With the inflammatory thickening of the tunica propria the elastic tissue practically entirely disappears from this layer and is greatly decreased in amount in the other laminae as well.

Cystic inflammation of the pelvis, ureter and bladder, then, is a condition about which the following facts seem established: First, it is primarily a disease of old age; second, it occurs in persons of either sex in whom a history of urinary tract disturbance or definite inflammation can be elicited; third, the cysts arise from degeneration of the lining epithelium, particularly that which has become cut off from the surface of the mucosa, the "cell nests" of von Brunn. The condition has occurred in several cases of double ureter and one of the writer's patients had this anomaly.

The profound disturbance in the epithelialization of the ureter incident to the formation of cell "nests," their proliferation and degeneration, and the almost constant factor of senility makes it indeed surprising that primary epithelial tumors of the ureter are so rare. Vesical polyps frequently contain many isolated groups of epithelial cells corresponding to von Brunn's "cell nests" and to them has been attributed an inflammatory origin in consequence (Saltikow).

Having in mind the large numbers of cell "nests" of von Brunn in the ureter and bladder of senile individuals and the high incidence of infections of the urinary tract in the aged, the writer believes that cystic inflammation of these organs is relatively common and not rare, as the literature seems to indicate.

#### SUMMARY

1. The condition described is a cystic inflammation of the pelvis, ureters and bladder.

2. It occurs in persons of either sex, in 95 per cent of cases in senile, arteriosclerotic individuals from whom a history of previous urinary inflammation or other disturbance can be obtained.

3. Three typical cases are reported in detail, all in aged men, two of whom had a history of prostatic trouble and the third bilateral pelvic calculi. In one a double ureter was present.

4. The pathogenesis may be epitomized as follows:

(a) In the aged, arteriosclerosis of the ureteral and vesical arteries occurs and is followed by muscular atrophy, fibrous myositis and loss of elastic tissue leading to atony of the ureter and bladder.

(b) By the marked infolding of the mucosa which follows, with fibroplasia in the tunica propria, many cell "nests" of von Brunn are formed.

(c) An inflammatory irritant, usually from the pelvis or bladder, causes the formation of granulation tissue which heals over apposed tips of mucosal folds to produce more cell "nests" (this being probably their only source in young individuals).

(d) The same irritant produces moderate proliferation of the isolated epithelial cells, followed by central degeneration

and fluid transudation, thus giving rise to microscopic and macroscopic cysts.

5. In view of the large number of cell "nests" of von Brunn in the ureter and bladder of senile individuals and the high incidence of urinary tract infections in the aged, the writer believes that cystic inflammation of these organs is relatively common in this class of patients.

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#### EXPLANATION OF PLATES

Figs. 1 and 2 are gross photographs. In Fig. 3 the section is stained with Mallory's aniline blue connective-tissue stain; in all the others Mallory's methylene blue and eosin was used. Fixation was in Zenker's fluid.



FIG. 1.—Case 1. Kidneys, ureters and bladder. The right kidney is atrophic and both have undergone extreme arteriosclerotic changes. The pelves and ureters show the extent of the cyst formation. The left ureter is double.



FIG. 2.—Double cystic ureter of Case 1. The macroscopic cysts suddenly cease at the junction of the ureters. Microscopic cysts are present as far as the vesical orifice.

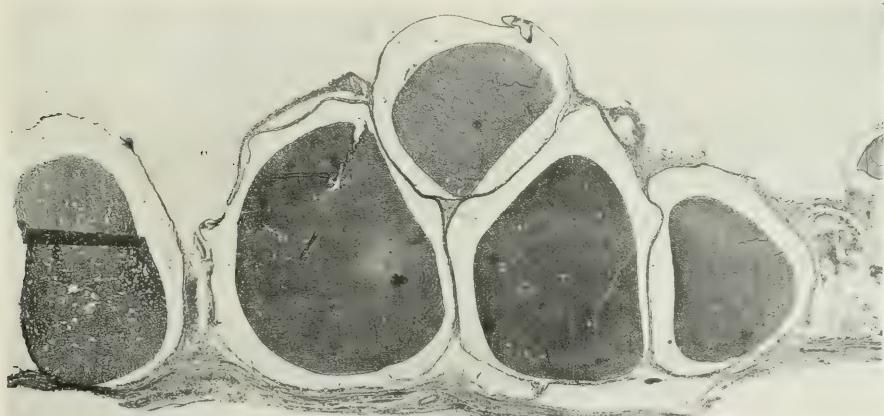


FIG. 3.—Longitudinal section of ureter from Case 1,  $\times 12$ . The thin walled cysts are filled with a colloid material in which are bodies formerly mistaken for protozoa, but which consist of nuclear fragments and cellular debris. Fixation has caused the cyst contents to shrink away from the walls.

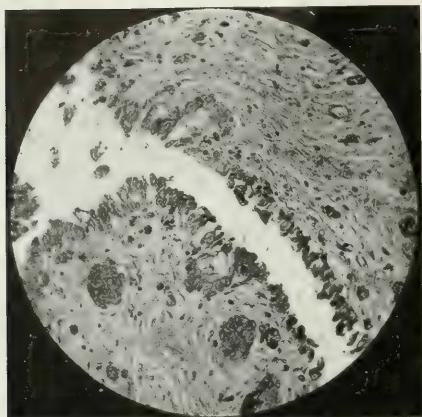


FIG. 4.—Section of the mucosa of ureter from Case II,  $\times 75$ . The formation of the cell "nests" of von Brunn is shown.

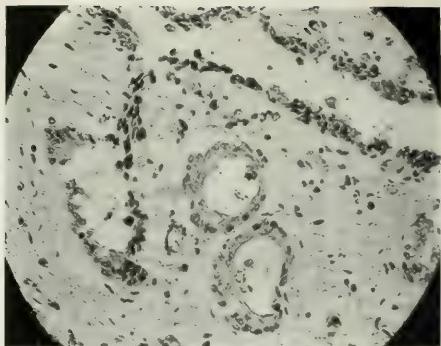


FIG. 6.—Portion of mucosa of ureter, Case III,  $\times 75$ . The infolding of the mucosa is well shown with healing over of the opposed folds by chronic inflammatory tissue with formation of cysts.

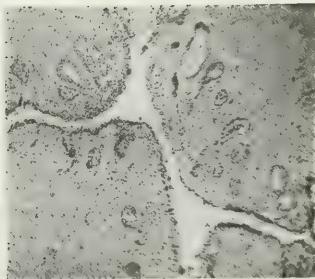


FIG. 5.—Mucosa of ureter from Case III,  $\times 55$ ; showing marked chronic ureteritis with production of cell "nests" and cysts. The epithelial lining has been largely destroyed.

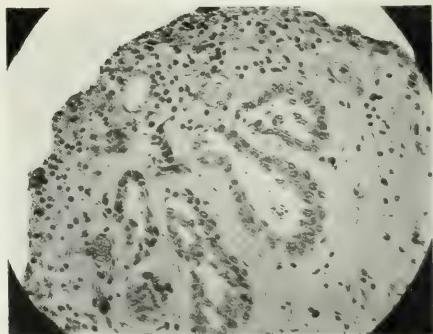


FIG. 7.—A fold of mucosa of ureter, Case III,  $\times 75$ ; showing marked chronic ureteritis and cysts.

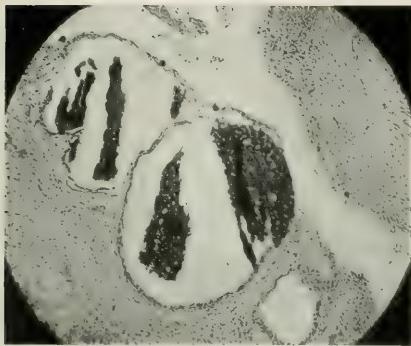


FIG. 8. The mucosa of ureter, Case III, -55. The section is through several macroscopic cysts with colloid contents similar to that shown in Fig. 3.

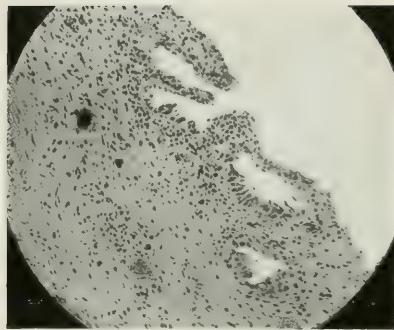


FIG. 10. A section of the bladder, Case II, -70. There is chronic cystitis with formation of microscopic cysts. Note epithelial "nests" cut off from the lining membrane.

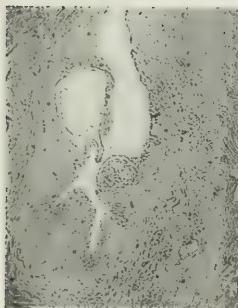


FIG. 9. Section of ureter, Case II, -45. The lining epithelium is destroyed by a small cyst arising from degeneration of the proliferated epithelium of the "nest"; a larger cyst is shown, its contents having been lost through faulty technique.



FIG. 11. The formation of macroscopic cysts in the same bladder as in Fig. 10 is shown. There is very marked inflammatory thickening of the tunica propria with fibrous myositis conspicuous throughout.

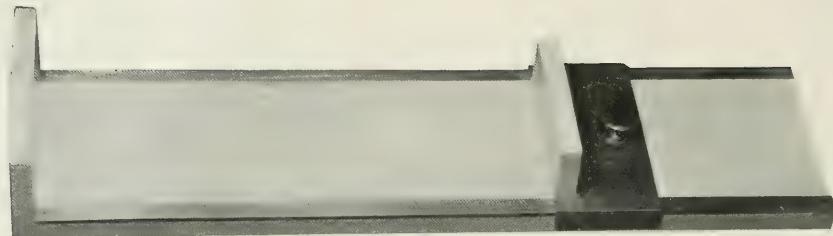


FIG. 1.—Apparatus for measuring the new-born. Constructed from maple wood and painted.

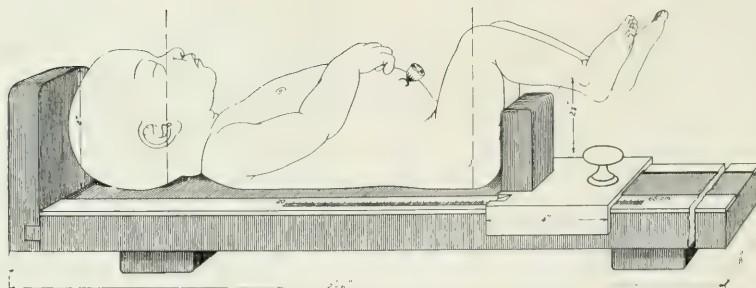


FIG. 2.—Schematic drawing of the measuring apparatus with baby in position for measuring sitting height.

## AN APPARATUS FOR MEASURING THE NEW-BORN

By ADOLPH H. SCHULTZ,

*Research Associate, Department of Embryology of the Carnegie Institution of Washington*

The size, particularly the length, of the new-born baby is of manifold interest. It has been shown to vary to a great extent, to average less in girls than in boys, less in negroes than in whites, and less in twins than in single-born individuals. Furthermore, the number of previous labors of the mother seems to influence the size of the fetus at term, primipare in general having smaller children than multipare. Variations in the size of the child depend probably also upon the size of the parents and the age of the mother. Numerous other factors, such as nationality, state of nutrition of mother, size and condition of maternal pelvis, etc., have been held responsible for differences in size of new-born infants or have at least been correlated with it. The length is also of great importance in determining the age of a baby, both full term or premature, and in this respect affords a more accurate criterion than weight.

The material upon which those investigations have been based was obtained in most of the cases from the records of obstetrical departments and was usually available in ample amount. However, there is one objection to the use of data relating to size from such records, and that is the method of measuring usually employed. This is only too often absolutely unreliable and very rarely accurate enough to approach scientific requirements. The measuring is frequently not done in a uniform way; suitable instruments are lacking, so that one has to be content with a tape (!), and the babies are not placed so that their positions are analogous in every case. The individual error in those measurements naturally must be very considerable and may amount to more than 10 per cent of the true measurement. Inasmuch as the above-mentioned differences in size under different conditions are mostly rather small and rarely surpass a very small percentage of the averages in length, it is easily seen that conclusions drawn from such crude measurements must be very unsafe.

In contrast to height (or length), the data on weight are very reliable, because here the technique is uniform, the required apparatus fairly accurate, and the chance for error minute. The contrast in accuracy of height and weight accounts partly for the apparently small correlation between the two measurements.

There is no reason why the height could not be obtained almost as accurately as the weight and this with no greater expenditure of time than heretofore. The only two requirements are uniformity of technique (especially of posing the baby) and a suitable apparatus. The former problem is best solved by answering clearly the question of what and how to measure. What one wants to measure is the dimension on the body of a baby, which best represents its size, or rather length. The choice here lies essentially between two measurements—the body length or standing height, and the crown-rump length

or sitting height. Most frequently the total length of the body, *i. e.*, from the soles of the feet to the top of the head, is taken. This measurement has two disadvantages: The baby's legs can only with difficulty be stretched straight, and the variable length of the lower extremity is included in the length of the head and trunk. The latter (sitting height) is individually less variable, being composed of fewer elements; it represents, furthermore, the true body length comparable to the body length of other mammals. The sitting height (from buttocks to top of head) should therefore be given first rank. The body height may be taken as a supplementary measurement, of interest mainly for comparison with the sitting height.

The position of the head, *i. e.*, whether it is bent downward or upward, as well as the direction of the thigh, influence the sitting height and should therefore be always the same. This question of how to measure can best be answered by following the custom of physical anthropology and placing the head so that a line through the outer opening of the ear and the lowest point of the orbit (ear-eye line) stands perpendicular to the main axis of the body. For measuring the sitting height the axis of the thigh should also be at right-angles with the axis of the body. In addition, attention has to be paid to the axis of the body or rather the curve of the back, which should be as nearly straight as possible. This is best accomplished by placing the baby on its back on a flat horizontal surface, the latter representing the body axis.

The author has designed a simple but accurate measuring apparatus (Fig. 1.), in which the above directions form guide points. This apparatus is now used with entire satisfaction for routine measuring in the obstetrical department of The Johns Hopkins Hospital. It consists in principle of a horizontal board on which the baby is placed on its back, of one perpendicular board firmly attached to one end of the horizontal or base board, which has to be touched by the top of the head of the baby, and another (sliding) perpendicular board, which can be brought into contact with the buttocks for the measuring of the sitting height or with the soles of the feet for measuring the standing height. The distance between these two perpendicular boards constitutes the required measurement and is read off from a scale attached to the horizontal board. The movable vertical board is mounted on a brass saddle, which slides on the horizontal board and holds the perpendicular board at right-angles to the main axis of the base board. On each of the two lateral edges of the base board a brass strip is inlaid and one of these is ruled in millimeters from 200 to 650, zero being at the end of the base board where it meets the firm perpendicular board. The range of ruling is sufficient for measuring from the sitting height of a fetus at the end of the sixth month to the standing height of an exceptionally large new-born. The brass saddle rests with its lateral

portions on the two brass strips; the center of the saddle is slightly raised to reduce friction to let only metal ride on metal. A small area on the edge of the saddle over the ruled brass strip, on a plane with the movable perpendicular board, is tapered to a knife-like edge to allow accurate reading of the scale. The chief dimensions of this apparatus are given in the schematic drawing of Fig. 2. The same figure shows the position of the baby when posed for measuring the sitting height. The apparatus can easily be made by any instrument maker or carpenter for a cost which should not exceed \$15 or \$20.<sup>1</sup>

<sup>1</sup> Where it is found impossible to have such an apparatus made, institutions desiring it may secure it in Baltimore by communicating with the author, at the Carnegie Laboratory, Johns Hopkins Medical School.

The apparatus forms certainly an improvement as compared with methods so far in use, and will enable one to measure accurately down to single millimeters. It is very desirable that this or some similar construction should be used by all obstetrical departments, in order to obtain in great numbers reliable data on the length of babies. Statistical treatment of such data in connection with various other factors to be found in histories will no doubt permit the drawing of a whole series of interesting conclusions. These will be the safer and more reliable the more accurately such measurements are made and the more material so treated is available; the latter factor being dependent on the number of institutions adopting this new method.

## AN UNUSUAL CASE OF TUBERCULOUS SALPINGITIS

By J. P. GREENBERG

(From the Gynecological Clinic of The Johns Hopkins Hospital)

The following case is one of interest because the condition was not recognized before operation, at the time of operation, nor even when the specimen had been removed. The diagnosis made from the history and the physical examination at the time of admission, was "tubo-ovarian abscess." The same opinion was held after examining the patient under ether, just before operation. After opening the abdomen, the diagnosis was changed to "tubal pregnancy, unruptured." The specimen, which was believed to be a tubal pregnancy, was taken to Dr. Streeter of the embryological department of the Carnegie Foundation. The true nature of the mass was not revealed, however, until it was opened.

### REPORT OF CASE

**History.**—G. C., Gynl. No. 25479, colored, aged 19, married, was admitted to The Johns Hopkins Hospital on November 17, 1919, complaining of pain, swelling and tenderness in the right lower abdomen. There was nothing noteworthy in her family history. Her general health had been good. She had had pneumonia at 14 and influenza at 18. Marked constipation had been present for many years. There was nothing of importance in the menstrual history save that during the first two days of the flow, there was moderately sharp pain on the right side. The last menstrual period occurred from November 11 to 15, 1919, the preceding one from October 12 to 16, 1919. No leukorrhea had ever been noticed. The patient had been married three years, but had never been pregnant.

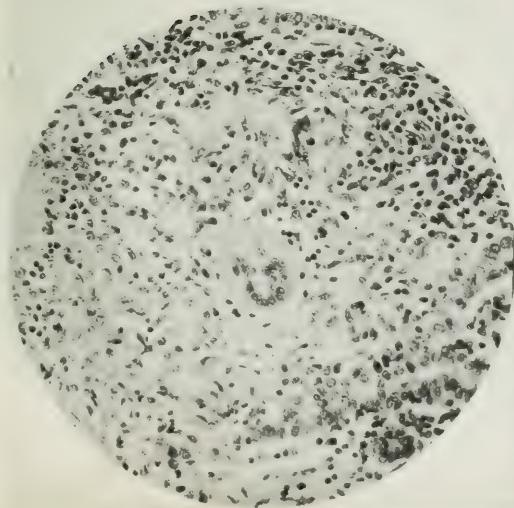
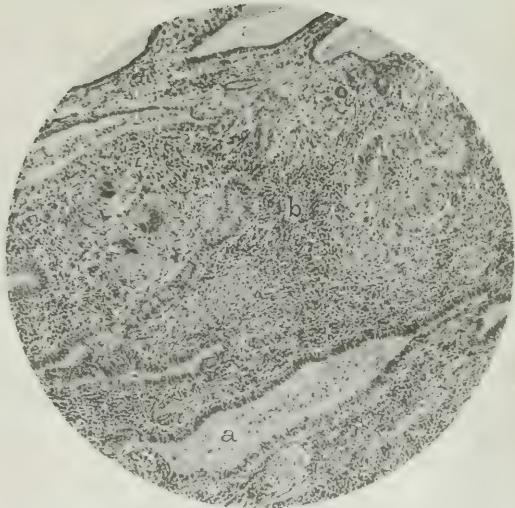
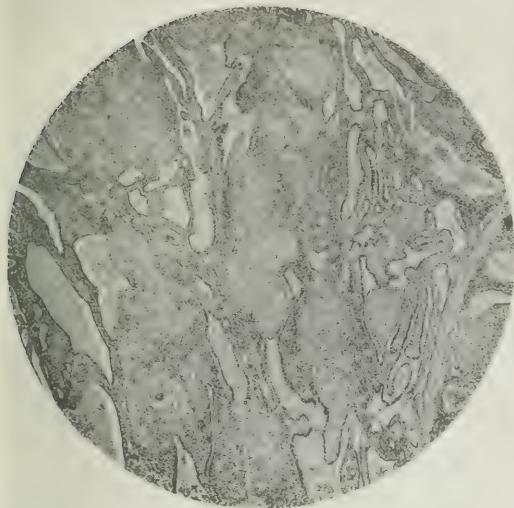
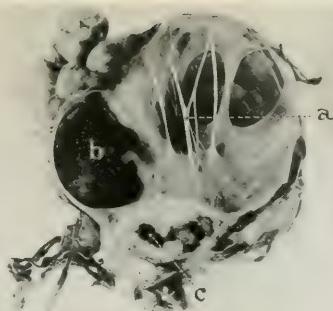
**Present Illness.**—Five years before the patient had had pneumonia and since that time there had been indefinite pains in the right lower quadrant. The pains were usually dull and dragging in character, but there had been acute exacerbations in which they were very sharp. The pains were localized in the right lower quadrant and did not radiate from that location. There had never been any nausea or vomiting. The pains had never been severe enough to cause the patient to go to bed until three weeks before admission. At that time, she was suddenly awakened in the night by very sharp pain in the right lower quadrant. She had had no discomfort at all before going to bed that evening. There was no nausea or vomiting and the patient did not faint. The pain only lasted a short while and the patient fell asleep again. The next day, the pain recurred and she remained in bed. On the following day, she got up and did her

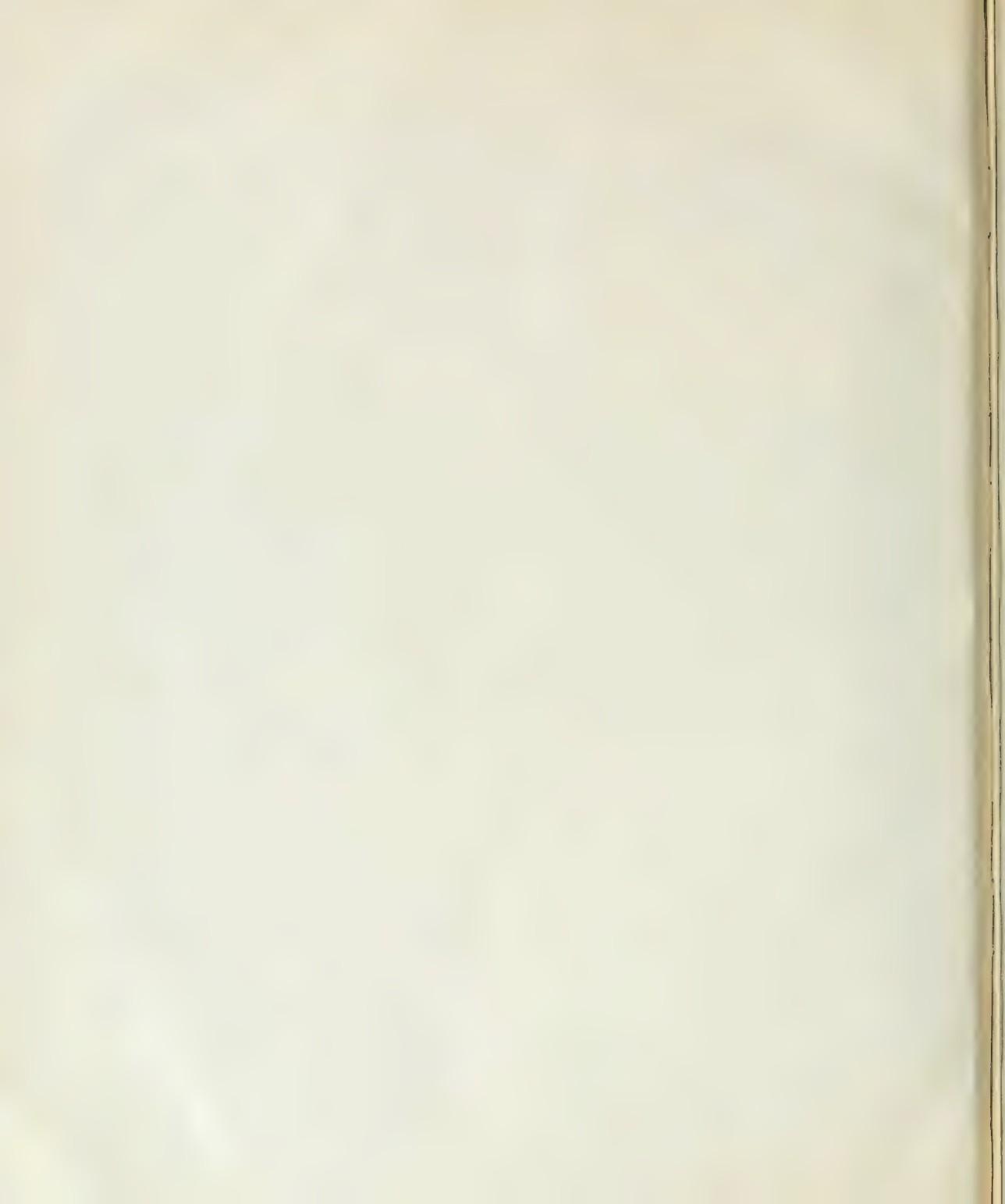
housework. The next day, she began to menstruate, this being the proper time for it. With the onset of menstruation, the sharp pain returned and the patient went back to bed. She remained in bed five days, during which time she menstruated and during which time, also, the pain in her right side persisted. After getting out of bed this time, she came to The Johns Hopkins Hospital Dispensary, to find out the cause of her pain.

**Physical Examination.**—The patient was a well-nourished and well-developed young colored woman in no apparent discomfort. The anterior and posterior cervical glands were enlarged. The lungs were entirely negative to inspection, palpation, percussion and auscultation. At the apex of the heart was heard a soft, blowing, systolic murmur, which was not well transmitted. The breasts did not show anything abnormal. Examination of the abdomen was entirely negative except for definite tenderness all over the lower part, most marked on the right side. On pelvic examination, the body of the uterus was found to be in mid-position, of normal size and consistency, but pushed over to the left side. Filling the right half of the pelvis and bulging into the culdesac of Douglas and also into the rectum was a tense, smooth, cystic mass, adherent and tender. No mass was palpable on the left, but there was slight tenderness in the right fornix. The temperature was 98°, the pulse 88, and the respirations 20. The R. B. C. was 4,096,000, the W. B. C. 9920, and the hemoglobin (Sahli) was 75 per cent. The blood-pressure was 118/80, the urine was negative, as was the Wassermann. The impression recorded from the above history and physical examination was, "chronic pelvic inflammatory disease with a tubo-ovarian abscess on the right side."

Under ether, the pelvic examination revealed the following: The body of the uterus was of normal size, in good position, and freely movable. On the right side were two masses which could be made out distinctly. The first mass was globular, with a diameter of about 12 cm., tense, rather cystic and absolutely adherent to the pelvic floor. Lying on top of this mass was a smaller one, oval in shape and measuring about 9 by 5 by 5 cm. The smaller mass was movable within limit and seemed hard. The left side of the pelvis was free. The left ovary was slightly enlarged, but freely movable. The diagnosis made from this examination was "tubo-ovarian abscess, right."

**Operation (Dr. R. L. Wharton).**—A pelvic puncture was done first, in the belief that the abscess could be drained. The peritoneal cavity was entered, but no fluid was obtained. As it seemed inadvisable to carry the pelvic operation any further, a midline





abdominal incision was made. Numerous adhesions were found and released without any difficulty or bleeding. Exposure being obtained, the uterus was elevated and found free from adhesions, of normal size and not softened. On the right side two masses were seen. The upper one was bluish in color, cystic, lobulated, and suggested an extra-uterine pregnancy in the outer one-third of the fallopian tube. This appeared to be just on the point of rupturing. By careful dissection, the mass was released, together with the entire length of the fallopian tube, from the mass underneath it. The tube with a wedge of uterine cornu was resected without rupturing (what we thought to be) the gestation sac. The lower, and by far the larger mass, proved to be a corpus luteum cyst. Since the entire cyst could not have been removed without injury to the ureter and rectum, only a portion of it was excised together with the right ovary. On the left side, the fallopian tube was somewhat enlarged and reddened and its fimbriated extremity was closed. As the ovary appeared normal, the tube alone, with a wedge of uterine cornu, was removed. One cigarette pelvic drain was placed through the drainage tract already present, the free end of the gauze lying in the sac of the corpus luteum cyst. The appendix was then removed.

#### PATHOLOGICAL REPORT

*Gross Description.*—The specimen consists of the right tube and ovary, the left tube and the appendix. The right tube is of great interest. *In toto*, it presents a typical picture of a tubal pregnancy (Fig. 1). The mass is egg-shaped, measures 8 by 5 by 4.5 cm. and is covered by very fine adhesions. For the most part, the mass is cystic and through the wall one sees a bluish-black discoloration, suggesting that of old blood. The inner portion of the mass consists of the uterine end of the tube and measures 5 cm. in length and 8 mm. in width. It feels very hard. On section, the lumen is found entirely filled with a grayish-white, homogeneous, firm material. The outer, and by far the larger, portion of the mass, consists of the remainder of the tube much dilated. The fimbriated end has been entirely sealed off. On cutting into the mass, one is surprised to find no blood. Instead, there is seen a greenish, gelatinous fluid, filling up a large cavity, crossed by numerous thread-like trabeculae (Fig. 2). On one wall of this cavity, adjacent to and apparently connected with it, is a discrete, rounded, rather firm mass, greyish-white in color (Fig. 3). This mass extends along almost the entire length of the cavity.

The left tube is coiled upon itself and measures 15 cm. in length. At its widest diameter it is 4 cm., and its entire surface is covered by adhesions. The fimbriated end is closed. At the uterine end, for a distance of about 2 cm., the tube measures 15 mm. in diameter and feels very hard. This same hardness is noted at the distal one-fourth of the tube. On section, these two hard areas disclose the lumen entirely obliterated by greyish-white, opaque, caseous masses, suggestive of tuberculosis. In the area of the tube between these masses, the lumen is markedly increased in size and contains a brownish, gelatinous, friable material, easily separated from the tubal mucosa. The latter is considerably thickened in scattered areas and is very much distorted.

The portion of the ovary present measures 5.5 by 4 by 2 cm. and is covered by adhesions everywhere. To one surface of it is attached a portion of the wall of a corpus luteum cyst. This cyst wall is 3 mm. thick and is easily stripped away from the ovary, save at one small area. On section, the ovary presents numerous small cysts.

The appendix measures 7 by 1 by .75 cm. and feels fairly firm. There are a few adhesions at the base, but none at the tip. Its blood-vessels are injected and the lumen is small owing to the thickness of the appendiceal wall.

*Microscopical Description.*—Sections through the right tube at about 4 cm. from the uterine end show a marked proliferation of tubal mucosa. The entire lumen is filled with an extraordinary number of villous projections which have fused with one another

so that no definite, continuous lumen remains (Fig. 4). The follicular spaces formed by this agglutination contain an abundance of small round cells, among which are found many polymorphonuclears. These spaces are lined with low columnar or cuboidal epithelium, which for the most part is intact and stains well (Fig. 5). Only here and there does one see degeneration or disappearance of epithelial cells. Scattered throughout the stroma are typical tubercles of varying sizes, in which are seen giant cells, epithelioid cells and a marked small-round-cell proliferation (Fig. 6). In a number of places necrotic masses are seen. The stroma shows a marked increase of fibrous tissue and is infiltrated with small round cells. Blood-vessels are few in number. The surrounding wall likewise contains definite tubercles and there is a generalized small-round-cell infiltration. All around the wall dense adhesions are seen. Sections through the caseous mass found in the cystic portion of the right tube (Fig. 3) show a picture similar to that just described, but in a much more exaggerated form. Conglomeration of the tubal folds is much more marked and much of the tissue is necrotic. In numerous places the epithelium has become degenerated and in some areas it has entirely disappeared. These sections show a much greater abundance of connective tissue. Typical tubercles are seen in the wall as well as in the interior of the tube.

The left tube presents a picture somewhat similar to that of the first sections described, but much less pronounced. In the middle portion of the tube, the lumen persists and is increased in size. Numerous tubercles are seen everywhere and there is extensive hemorrhage into the lumen. Around the wall of the tube are dense adhesions. Sections through the proximal and distal ends of the tube reveal similar findings, except that the lumen has been obliterated by the agglutination of folds.

The ovary shows the corpus luteum cyst wall, some hemorrhage into the stroma and adhesions on the surface.

Sections through the appendix show round-cell infiltration; those from the proximal portion showing adhesions in addition.

*Diagnosis.*—Tuberculous salpingitis, bilateral; chronic appendicitis; corpus luteum cyst of right ovary.

*Course in Hospital.*—The convalescence was somewhat stormy due to a post-operative pneumonia which developed on the second day after operation. The condition cleared up entirely. The patient was discharged December 16, 1919, and the note made was as follows: *Abdomen:* Incision healed *per primum*. *Vaginal:* Normal except for a hard, round, insensitive mass in right fornix, the corpus luteum cyst, which is absorbing. Temperature during the last few days not above 98°.

I wish to extend my thanks to Dr. Thomas S. Cullen, through whose courtesy I am permitted to report this case and to Mr. Osborne O. Heard for the splendid photomicrographs.

#### EXPLANATION OF PLATE

FIG. 1.—The right tube as removed at operation. *a* shows the uterine end, *b* the mass mistaken for a tubal pregnancy.

FIG. 2.—Cross-section through the mass, Fig. 1, *b*, showing the trabeculae, *a*, and the cavity, *b*. At *c*, the lumen of the tube is seen.

FIG. 3.—Cross-section through the mass to show the greyish-white tumor, *a*, and the cavity, *b*.

FIG. 4.—Photomicrograph of section through the right tube, 4 cm. from the uterine end, showing the marked proliferation of tubal mucosa with no definite, continuous lumen.

FIG. 5.—Photomicrograph of section through the caseous mass. This area shows the follicular spaces, *a*, lined with columnar epithelium. Small-round-cell infiltration is seen at *b*.

FIG. 6.—Photomicrograph through the caseous mass. A typical tubercle is seen, showing a giant cell, epithelioid cells and small-round-cell infiltration.

FIG. 7.—Magnification of central portion of Fig. 6.

## PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

FEBRUARY 2, 1920

The Production of an Acute Respiratory Disease in Monkeys by  
Inoculation with *B. influenzae*. DR. FRANCIS G. BLAKE.

Following the discovery by Pfeiffer of *B. influenzae*, this organism was generally accepted as the cause of epidemic influenza. Objections to this theory, however, arose when *B. influenzae* was found to be present in the normal mouth and to be associated with other diseases of the respiratory tract, such as, measles, bronchitis, bronchiectasis, etc. Some observers have gone so far as to say that the influenza bacillus was a saprophyte and had no pathogenicity for man. These objections have little weight since it has been quite thoroughly established that many organisms, whose etiological relationship to respiratory diseases is proved, have been found in normal mouths and have been associated with other pathologic processes. It has furthermore been established that *B. influenzae* is pathogenic for man, since it is found in cases of meningitis, bacterial endocarditis, pneumonia and other diseases. During the recent pandemic the failure of some bacteriologists to find the influenza bacillus in a certain number of cases led to scepticism as to the etiologic rôle of this bacillus in influenza, and it was relegated to the position of a second invader along with the pneumococcus and other complicating organisms, and the theory was advanced that a filtrable virus was the cause of the disease. Nothing in the way of experimental evidence having been advanced that a filtrable virus is the cause of the disease, we have thought that the influenza bacillus could not lightly be dismissed and relegated to a secondary position. As there was no proof that the influenza bacillus was not the cause of the disease, it seemed desirable to try inoculation experiments on animals to determine what rôle *B. influenzae* played in the disease, for it has certainly played an important part in the epidemic.

The series of animal experiments was undertaken with Dr. Cecil at the Army Medical School, in Washington. It was clear that previous results obtained by different observers were often very conflicting. It was also evident that the majority of previous animal inoculation experiments had little direct bearing on the possible relation which the influenza bacillus might have to influenza, since most of the inoculations had been intraperitoneal, subcutaneous or intravenous, and it was not to be expected that the disease which is a respiratory infection could be produced in animals by other paths than the natural path of entry in man. It seemed, therefore, that if we were to obtain information as to the rôle of *B. influenzae* it would be necessary to inoculate the mucous membrane of the respiratory tract. It also seemed to us that probably the lack in results from animal inoculation experiments might be largely due to our meager knowledge of the influenza bacillus, and also to the failure to take into consideration that such pathogenicity as the bacillus possesses is easily lost outside of

the body. Because the means that we have for distinguishing between possible pathogenic and saprophytic strains are entirely inadequate, it was decided in our experiments to use one strain, one that had been given us by Dr. Rivers and that had been isolated in pure culture from a case of empyema following a case of influenza. It has been discovered that the monkey was the best subject, and these animals were used for the experiments. The animals were fresh stock, which had recently arrived. They were thoroughly healthy, normal animals, and we used no means to injure the respiratory tract in any way in advance, before inoculation. As is well recognized, the use of monkeys in the production of infectious diseases requires caution in the interpretation of temperature and leucocyte changes as indicative of infection in the absence of other supporting evidence. This is particularly so with *B. influenzae*, because the toxic effect of influenza bacillus cultures and culture filtrates are such that care has to be taken that the results obtained are from actual infection and not from the temporary intoxication. In our experiments temperatures and leukocyte counts were taken daily, clinical symptoms recorded, cultures from the nose and throat and blood made. Since none of our cases were fatal, most of the animals were killed either in the acute stages of the disease, or while convalescing, and autopsies with bacteriological studies were made. The bacillus used was isolated from a chronic empyema fluid, following a case of influenza. It was demonstrated to be a Gram-negative, non-motile, hemoglobinophilic bacillus. When it was received it had been in culture for about 6 weeks, on artificial media and was avirulent for white mice. In a preliminary test a monkey showed no evidence of infection and it was evident that the organism would have to be raised considerably in virulence before successful results could be obtained. This was done by animal passage, through a series of 11 white mice and then through 13 monkeys by intraperitoneal inoculations. It was found at first that *B. influenzae* began to disappear from the peritoneal cavity of the inoculated mice by the end of 8 hours and was gone entirely by the end of 24 hours. Consequently the mice were killed after from 6 to 8 hours. After the organism had been passed through 11 mice, monkeys were substituted. The monkeys showed great variation in reaction to intraperitoneal inoculation. The symptoms were those of peritonitis and severe intoxication with leucopenia. At the completion of the series of intraperitoneal inoculations the organism was found to be fairly virulent, 0.01 c. c. of a blood-broth culture killing mice within 48 hours. This virulence was easily lost on culture outside of the body, and it was therefore necessary to use cultures but recently removed from the previous animal. For inoculation of the respiratory tract the material consisted of first or second subcultures taken from the peritoneum of a monkey dying from influenza peritonitis or from the respiratory tract of those having influenza pneumonia, or of the peritoneal exudate

from those dying from influenza peritonitis. The culture media were chocolate-agar plates or blood-broth. In using peritoneal exudate the purity was controlled by direct smears and culture. It is impossible to state whether one method gave better results than another. Two modes of inoculation were employed. In one inoculation was made in the upper respiratory tract to determine whether *B. influenzae* could initiate an infection of the upper respiratory tract, and if so, what the nature of the infection might be. In the other inoculations were made directly into the trachea. The purpose of this was to study the pathologic characteristics of the pneumonia if such were produced. It seems wise to present these two series of experiments since they are of quite different significance.

We will take up first those inoculated in the upper respiratory tract. Twelve monkeys were inoculated in the nose and mouth. The amount of culture or peritoneal exudate varied. Four monkeys were inoculated simply by swabbing the mucous membranes with an applicator previously dipped in the culture, 2 monkeys had 0.25 c.c. in each nostril and the mouth, one had 0.5 c.c. in each nostril and the mouth, 2 had 0.8 c.c. in each nostril and the mouth, and 3 received 1 c.c. in each nostril and the mouth. In each instance there developed an acute respiratory infection of from 3 to 6 days' duration. The severity of the diseases bore no apparent relation to the amount of material used in inoculation. The onset of symptoms occurred quite suddenly from 3 to 6 hours after inoculation. The first symptom in all cases was a varying degree of prostration, often extreme, the monkeys lying prostrate on the floor of the cage, and sometimes pressing the hands tightly over the top of the head. This symptom was quite different from the symptoms of the onset of pneumococcus pneumonia in monkeys. In that disease there was never prostration at the onset, the disease being detected only by temperature rise, leucocytosis and accelerated respirations. In the influenza cases, simultaneously with the appearance of prostration, there was an abrupt temperature rise in some cases, but in others there was practically no fever. The symptoms of the respiratory tract infection soon followed; frequent sneezing, rapid blinking of the eyes, suggesting possible photophobia, and rubbing of the nose occurred. The subsequent course of the disease was in general that of a self-limited, respiratory disease, the acute stage of which lasted from 3 to 6 days. Three monkeys were allowed to survive and in these a considerable degree of weakness which lasted for some time was observed. By the end of from 24 to 48 hours the infection had spread from the upper respiratory tract to the lower respiratory tract, which was evidenced by a cough. This was again quite different from the cough of pneumococcus pneumonia in monkeys. In the lobar pneumonia cases the cough was slight and developed late in the course of the disease. In the influenza cases the cough was severe and very frequent. About this time a variable amount of mucoid exudate began to be excreted from the nose of the monkeys. In some cases this became muco-purulent later on, but in some it remained mu-

coid and scanty. Smears of this made 24 hours after inoculation not infrequently failed to show the influenza bacillus. The temperature reaction varied greatly and showed no constant curve. One feature of this temperature curve which was fairly constant was a fall in the temperature on the third day with a subsequent rise. Leucocyte counts showed either a definite leucopenia or no significant total variations from the normal. The differential count showed that there was an initial increase in polymorphonuclears of short duration which rapidly fell to a normal or subnormal. In 3 cases only did leucocytosis develop, and that on the third or fourth day in association with an acute purulent sinusitis. No great stress can be laid on the variation in the leucocyte count, but the absence of leucocytosis which has invariably occurred following intratracheal inoculations with Pneumococcus or Streptococcus hemolyticus would seem to be of some significance. The complications that occurred in this series are of considerable interest. An acute purulent sinusitis developed in 5 cases, this condition being quite analogous to the sinusitis which complicates influenza in man. Cultures from the antra showed abundant influenza bacilli in 3 cases, a moderate number in 1 case, and none was recovered in 1 case. Two monkeys developed a recognizable pneumonia in 3 or 4 days. The onset of the pneumonia was insidious, and the disease was suspected only by a rise in temperature and respiration rate. At autopsy *B. influenzae* was discovered in pure culture in the lungs. A third case of pneumonia found on pathological examination was so slight that it was not recognized during life.

The second group, in which the inoculations were made into the trachea consisted of 10 monkeys. Of these 7 got pneumonia, 2 tracheobronchitis without actual pneumonia and another resisted infection altogether. In 2 cases infection passed from the lower respiratory tract into the upper tract with the usual developments of sneezing, rhinitis, etc. None of these cases was fatal. One animal developed septicaemia and pericarditis. Cultures from the lungs at autopsy showed the presence of influenza bacilli in pure culture.

The pathologic lesions cannot be shown by lantern slides. At autopsy the mucous membranes of the nasal cavity were swollen, injected and bathed in mucoid or mucopurulent exudate. The antra presented a similar appearance and contained a mucopurulent exudate. Histological sections show edema and congestion of the mucosa, swelling and desquamation of the epithelium and infiltration with leucocytes and lymphocytes. The mucous membranes of the trachea and bronchi showed a similar inflammatory process. In the monkeys with pneumonia there was an intense bronchiolitis. The pneumonia was characterized by its widespread distribution, intense bronchitis and bronchiolitis, areas of peribronchial consolidation, wide-spread hemorrhage, and a marked patchy vesicular emphysema. The pleurae were only slightly or not at all involved. In one case very marked dilatation of the bronchi approaching bronchiectasis occurred. The influenza bacillus was recovered from the nasal mucous membranes, the antra, the trachea and the bronchi, either in pure culture or in association with other

bacteria that are normal inhabitants of the upper respiratory tract of monkeys. From the lungs it was recovered in pure culture.

In summarizing it is desired to lay particular stress upon the results obtained in the series of 12 monkeys inoculated in the upper respiratory tract. This series of experiments has shown that *B. influenzae* can initiate in normal animals an acute infection of the mucous membranes of the upper respiratory tract which may spread by continuity to the lower respiratory tract; that the disease so produced is characterized by sudden onset with prostration, and is accompanied by either a leucopenia, or an absence of leucocytosis, and that it runs a self-limited course of brief duration. It may be complicated by acute purulent sinusitis and a type of bronchopneumonia which has been ascribed to influenza bacillus infection of the lungs of man. Control experiments with highly virulent pneumococci and hemolytic streptococci have shown that these organisms do not possess the property of initiating an infection of the normal mucous membranes of the upper respiratory tract and that they must be introduced into the lower respiratory tract before they will initiate infection. This group of experiments is believed to be evidence in favor of the possible primary etiologic rôle of *B. influenzae* in influenza.

The second group of experiments is of little significance in this respect. They do serve to show, however, that the type of pneumonia in man that has been ascribed to infection with *B. influenzae* can be satisfactorily reproduced in monkeys with the organism and therefore complete Koch's postulates with respect to bacillus influenza pneumonia.

#### DISCUSSION

DR. A. L. BLOOMFIELD.—It is very interesting to hear of this disease which has been produced in monkeys by the influenza bacillus. As Dr. Blake describes it, it seems to resemble influenza, but I should not be at all prepared to accept it as identical with the epidemic disease seen in man. We are still in doubt as to the relation that the influenza bacillus has to the epidemic disease.

When the epidemic first appeared in 1918, the main evidence in favor of the influenza bacillus was its presence in almost every case. Since the epidemic of last winter, however, many observers have had ample opportunity to see that the influenza bacillus can be recovered from the normal mouths of healthy individuals in many cases if proper media are employed. In the second place, as Dr. Rivers has shown by his work, we are dealing with a great variety of organisms, a large group, so that until this group is separated out into its various component strains, it seems barren to discuss the relation of the influenza bacillus to the disease.

I do not believe we can altogether neglect the negative experiments which are carried out by Leake, Rosenau and others, who inoculated healthy people with the secretions from actual cases as well as with freshly isolated strains of influenza bacillus. In none of these individuals was epidemic influenza produced.

DR. W. G. MACCALLUM.—Dr. Blake's description of the pathological lesions produced by the introduction of the influenza bacillus are interesting because the lesions are so familiar. They are exactly those that we found in the pneumonias following influenza which were caused by the influenza bacillus. But he concluded by saying that these are the lesions found complicating pneumonia following epidemic influenza, and I do not agree with that, because we found very different forms of pneumonia after epidemic influenza according to the bacteria concerned. While this type resulted when the influenza bacillus was present alone, a very different pneumonia was found when it was due to the pneumococcus, and this in turn was quite unlike that produced by a hemolytic streptococcus.

We have learned that the type of pneumonia depends very strictly upon the nature of the predominant secondary or bacterial invader, and upon the state of resistance of the individual. In the cases in which the influenza bacillus is the secondary invader, there is a considerable induration about the bronchioles, involving the neighboring alveoli. It is an interstitial bronchopneumonia only slightly different from that produced after measles by the hemolytic streptococcus. But in a few cases in which resistance seems to have failed, the peribronchial infiltration is slight and is masked by a great outpouring of blood.

The extraordinary pathogenicity of the influenza bacillus used by Dr. Blake is very striking, but I do not see that it throws any light upon the nature of epidemic influenza to demonstrate that the influenza bacillus like the streptococcus is a serious pathogenic agent. The experiments show that a febrile reaction with prostration and leucopenia can be produced in animals, but those are also effects of other bacteria, and the one character of epidemic influenza which is easily recognizable, its explosive spread through the population, is of course not evident.

DR. T. M. RIVERS.—It is needless to say that I am very much interested in Dr. Blake's work. He has been kind enough to inform me from time to time of his progress. I think he has demonstrated experimentally what was known in 1897, for at that time Meunier reported a series of cases of pneumonia from which pure cultures of *B. influenzae* were recovered from the blood and lungs, both before and after death (lung punctures were employed to obtain cultures before death). I should like to think that the influenza bacillus caused the epidemic, because that is the only tangible thing we have at present. If influenza is not caused by the bacillus, we must put this disease on the shelf with measles, scarlet fever, smallpox, and such diseases, and that shelf is already full enough.

In the first epidemic, 1918, *B. influenzae*, when looked for properly was found in 100 per cent of the cases, and in this epidemic, 1920, it has been found in 120 per cent, that is, often *B. influenzae* of more than one kind has been recovered from the same mouth. The group of Gram-negative hemoglobinophilic bacilli is certainly a large one which can be subdivided by cultural characteristics. Some are hemolytic,

and if "chocolate agar" or Avery's medium be used exclusively, the hemolytic ones will be carried side by side with the non-hemolytic ones and the bacteriologist will be none the wiser, calling them all influenza bacilli.

It is very likely that these bacilli will be grouped culturally and immunologically. So far only one constant group has been made out and that is the meningitic one. Seven strains have proven to be alike culturally and by agglutination tests. From the throats of normal people and influenza patients an organism has been obtained a few times which was similar to the ones in the meningitic group. The bacillus with which Dr. Blake was working probably falls in the meningitic group. It was obtained in pure culture from an empyema in a child and agglutinated 1-1280 with a serum made by immunizing a rabbit against a meningitis strain, the titer for the homologous strain being 1-2000.

The presence of the influenza bacilli in 100 per cent of the cases of influenza does not prove that it is the cause of the disease any more than the presence of *B. coli* in 100 per cent of the stools of typhoid patients proves that it is the cause of typhoid fever and vice versa. It will be necessary to group these organisms and then definitely link a certain strain or strains with the disease influenza before their etiological claims can be established. At present the proof still seems to be lacking.

Someone might be cruel enough to ask Dr. Blake how he knew the bacillus recovered after passage through mice and monkeys was the same as the one sent him. Supposedly it was, I hope Dr. Blake is right.

**DR. W. H. WELCH.**—Dr. Blake, it seems to me, has foisted every criticism which may be raised. Whatever may be the relation of the organism to the epidemic disease, he has certainly made a very interesting and valuable contribution to the study of the pathogenic character of the influenza bacillus. The prevailing view has been that the influenza bacillus is a secondary invader like the pneumococcus and other organisms. When we saw the first autopsies in 1918, I was impressed by a certain characteristic of the lesions; these wet, haemorrhagic, soggy lungs and the bronchopneumonic types. Dr. MacCallum has shown me some with dilatation of the atria and marked hyalinization of the epithelial lining. This showed up very clearly with a good acid strain. It has been found that this occurs also in the pneumonia produced by gas poisoning, and also in the experimental pneumonia produced by various chemicals. There was a coagulative necrosis in which the nuclei of the cells lining the dilated atria of the lungs had disappeared. I do not claim that they are present in all cases, but I should like to see them in some case which is under suspicion or which is known to have been caused by the influenza bacillus. I only know of one definite characteristic of this disease, and that is that it spreads like wildfire. It may be that we have scattered, abortive cases, which light up occasionally into epidemics, but we have no means of recognizing these scattered cases if they do exist. It is the rapid spread over large areas of country that makes it

so extremely discouraging to work with experimentally. We have no test that we can apply and say "here is influenza." If the influenza bacillus is the cause of the disease it must be some strain with some cultural characteristic which we are at present unable to identify. I am distressed to learn that the influenza bacillus that Dr. Blake is dealing with falls into the group of meningitis bacilli. I should have said that it would fall in with any other group or strain than the meningitis strain. There are reasons why I think one is justified in taking a position that some strain of the influenza bacillus may be the cause of the epidemic influenza. I think that this epidemic is likely to pass away and we are no more familiar with the control of the disease than we were in the epidemic of 1899. It is humiliating, but true.

**DR. F. G. BLAKE.**—I wish to agree with many of the criticisms that have been made. I have no desire to advance these experiments as proof that the influenza bacillus is the cause of epidemic influenza but merely as evidence in favor of it. I am quite certain that they do not prove it. I think Dr. Welch is right when he says that the only way to prove it is to produce an epidemic in a large group of healthy men. I think all arguments concerning the pathologic characteristics of the lesions in the pneumonia cases is entirely beside the point in considering the question of primary etiology. The important point is that the influenza bacillus can initiate an infection of the upper respiratory tract producing a disease essentially like influenza in man, whereas other organisms commonly found in influenzal pneumonia cannot do so, in monkeys at least. This does not prove that it is the cause of influenza, but appears to us very suggestive evidence. It is an experimental demonstration that the syndrome of influenza in man can be produced in monkeys by inoculation with *B. influenzae*.

With regard to the hyalinizing membranes of the atria, we looked for it in our monkeys, but did not find it. This result we attribute to the fact that the cases which exhibited the lesion were very severe and rapidly fatal, extremely virulent. In our monkeys we were unable to produce a form virulent enough to produce the hyalinizing membrane.

FEBRUARY 16, 1920

**1. Presentation of Two Cases of Epilepsy Apparently Cured by a New Form of Operative Treatment. DR. WALTER E. DANDY.**

These cases are presented to the Medical Society in order to demonstrate the results of a new treatment for epilepsy. From observations made at numerous operations upon the brains of epileptics I have come to the conclusion that epilepsy is due to a definite lesion of the brain, and am encouraged to a hopeful outlook for its treatment.

The first patient is a miner, thirty-four years of age. Until the onset of his present illness he has been perfectly well. Briefly, his illness may be summarized as follows: Six months ago, without any warning, he was suddenly seized with a convulsion, which began in the right half of his tongue, the right side of his face; and passing down the right arm and leg, soon involved the entire body. He was unconscious for probably

a few minutes; and after recovering from the attack he had a marked defect of speech and a weakness of the right arm and leg. These sequelae soon cleared completely, but a series of *petit mal* attacks supervened and have persisted with equal severity but increasing frequency until the time of admission. After he came under our care the attacks were remarkably constant in type and had a most striking periodicity. Every three minutes day and night a characteristic jerking would begin in the right side of his tongue and face and persist in this sharp localization for fifty to sixty seconds. During each twenty-four hours, therefore, about 250 of these attacks developed, there being no mitigation during sleep. A little dysarthria was noted, but quickly disappeared. There was no progression of the attack beyond these precise limits and no loss of consciousness. The third and fourth year students have seen these attacks in ward rounds and clinics, and will quickly note the change in his condition. The diagnosis of Jacksonian epilepsy was apparent.

An exploration of the left cerebral hemisphere disclosed a sharply defined lesion in the pre-Rolandic area, in the region of the second and third frontal convolutions, Broca's area, the face and tongue center. In these regions the pia-arachnoid membrane was greatly thickened, giving a markedly opaque covering over this part of the brain. Under this thickened membrane there was a considerable accumulation of fluid which had a distinctly yellow tint. When the membrane was pricked and the fluid released it was quite evident that the surface of the underlying brain had become softened, and in one area, about  $1 \times 1$  cm. it was very definitely of a brownish color. Below this superficial coat of softened cortex, the brain showed no discernible change. The entire affected zone of brain and the superimposed membranes and the subarachnoid cyst covered an area probably  $6 \times 6$  cm. Elsewhere the brain and its coverings were apparently normal. The sharp delineation of the affected area and the contrast to the adjacent normal brain were easily apparent, even to an inexperienced eye. There could be no doubt that such a sharp lesion so precisely located must have an etiological bearing upon the production of these focal attacks.

A lesion of this character, I believe, is to be found in most cases of epilepsy. It is frequently localized, although often in severe cases the entire surface of the brain may be involved. How it brings about the attacks is largely conjectural. It seems probable that direct implication of the pyramidal tract by this lesion is responsible for the motor manifestations of the epileptic seizures. The cerebrospinal fluid accumulation forming a subarachnoid cyst may be the inciting agent and account for the periodicity of the attacks; that is, the circulation of fluid by filling and discharging seems to account for the onset of the attacks and the latent period, respectively. Working on this assumption, the rational treatment would appear to be the permanent obliteration of the cyst so that it could not refill with cerebrospinal fluid and "set-off" the pyramidal tract. From experiments on animals it was found that iodine efficiently obliterated the subarachnoid space. In this patient the cystic areas were

opened with a needle, the fluid released, and the spaces injected with iodine. The irritant action caused adhesions in the course of a few days, and consequently a permanent closure of the cyst. Since the lesion in this patient involved Broca's area, we could not avoid producing temporarily a complete motor aphasia (direct action of the iodine). This has since cleared up completely. The day following the operation the patient had a general convulsion and one or two focal seizures, but since then (it is now twenty-five days since the operation) there has been no semblance of an attack.

Two years ago I used this operation for the first time on a boy eight years of age with focal epilepsy. He had had four or five attacks daily for several years prior to the operation. A few attacks persisted for several days after the operation, but at the end of two weeks they had entirely ceased and have not returned to date (two years). The same pathologic lesion of the brain was found and the same iodination performed. I know of no other cases of epilepsy with a similar history which have gone this length of time without an attack after any medicinal or operative treatment. However, in view of a certain capricious nature of the disease, it is too much to presume that this treatment will prove successful until many more cases have been treated and a longer time has elapsed; the results in these cases, however, are too striking to be explained as coincidental.

**2. An Unusual Instance of Ventricular Escape. DR. E. P. CARTER.**

**3. The Relationship Between Alkali Retention and Alkali Reserve in Normal and Pathological Individuals. DR. W. W. PALMER.**

It is now well known that the chief mechanism in the blood for maintaining a constant reaction is the balanced solution of the carbonates. The bicarbonates are in the blood in about a 0.03 molecular solution, or when estimated as free  $\text{CO}_2$ , about 55 to 70 volumes per cent. Normally, this bicarbonate level in the blood is maintained with extraordinary constancy. This is effected by the renal and lung mechanisms. When the bicarbonate level in the blood diminishes by reason of a pathological process going on in the body or by reason of the mechanism which regulates this level breaking down, there is a reduction of the level of sodium bicarbonate in the blood. This condition, you remember, has been called *acidosis*, and is generally so called now, or, by the more recently introduced term, *reduced alkaline reserve*. The use of sodium bicarbonate to correct this state of acidosis was first introduced by Stadleman in 1883. He, as you will remember, was the first investigator to discover an abnormal acid in diabetes urine. Ever since he introduced the use of bicarbonate, it has been used a great deal, not only for acidosis, but in a great variety of instances in clinical medicine. It has been also observed for many years that the administration of sodium bicarbonate will produce after a time a strongly alkaline urine. The amount necessary to accomplish this has been noted to be quite variable. No particular attention had been paid to this fact until in 1912

Sellards, working in this clinic, studied the effect of sodium bicarbonate when administered in nephritis, particularly chronic nephritis, and found that it could be used more or less as a crude measure for the degree of acidosis. At the time the criterion for the effect was the reaction of the urine to litmus. Independently, and without knowledge of Sellards' studies, working with Henderson, I observed the same fact and that it could be used as a measure for acidosis in a very crude manner. The criterion that I used was the variation of the hydrogen-ion concentration in the urine. It was found that in any individual, where the blood bicarbonate was normal, the ingestion of a small amount would markedly influence the hydrogen-ion concentration in the urine within an hour, while in pathological cases, where there was known to be an acidosis, a large amount was necessary before any influence on the urine was noted. This was a crude method, but we were looking for some simple test which could be used clinically, and we also recognized the fact that renal function may play a very important rôle in this phenomenon, and that, instead of measuring acidosis, the kidney might throw us off the track by not excreting the alkali until we had given more than was necessary. At that time there was no good method existing for measuring the blood bicarbonate directly. In 1915 an apparatus was devised by Van Slyke by which blood bicarbonate could be measured in the blood. It was noted in 1915 that the kidneys acted nearly normally in response to bicarbonate in cases of severe nephritis, where large amounts of an alkali were necessary before any effect could be noted in the urine. After this the alkali was stopped, the urine allowed to come back to its former acidity, and then one dose of 5 gms. given. Then the kidneys reacted as in a normal case. We thought this a good criterion and that a good check on this method would be to study the relation of the alkali retention to the alkaline reserve. This was done. The method of experimentation was very simple indeed. Blood was withdrawn about two hours after a meal, the bladder emptied, the pH determined, sodium bicarbonate administered in about 2 gm. doses at half-hourly intervals until the effect of the sodium bicarbonate was manifest. It was our purpose to reduce the action of the urine to the reaction of the blood. It was found that when the reaction of the urine had been depressed to the reaction of the blood, then the blood bicarbonate level varied within the upper limits of the normal, that is, about  $70 \pm 5$  volumes per cent. In pathological cases we found quite a different state of affairs. When the urine was depressed to the reaction of the blood, the blood bicarbonate was much above the normal limits. In one case 104 volumes per cent was found. We were most fortunate in not encountering any unpleasant effects in our work, for since then we have heard of several cases in which tetany was induced by the use of large amounts of sodium bicarbonate. We found that the only desirable way to control it was by the  $\text{CO}_2$  determinations in the blood. At the Presbyterian Hospital, with the assistance of Dr. Salvesen, this work was carried still further. The object was to find what the blood bicarbon-

ate level would be if taken at the time when the urine showed its first effect. We have studied 24 pathological cases, taken from a variety of conditions. In the 24 cases we found no case in which the bicarbonate was at a dangerous level, and practically all were within the upper limits of normal. This seemed to me most important in a good many ways. For instance, it is not always possible to control the administration of sodium bicarbonate in cases of known acidosis by methods that we are able to use in a well-organized hospital, where we are able to determine frequently the blood bicarbonate, but in general practice it does give a simple method of controlling the administration of alkali and makes such administration perfectly safe. There is the possibility of producing tetany by the use of too much bicarbonate, and it is not desirable to give any more than is necessary by mouth because of the gastro-intestinal symptoms that may arise. If enough alkali be given to depress the urine below the reaction of the normal blood, albuminuria may be produced, which, of course, can be cleared up rather quickly if the sodium bicarbonate be discontinued. It is not my purpose to take up the use of bicarbonate, but to point out the fact that it may be used safely in a very simple way.

#### DISCUSSION

DR. JOHN T. KING, JR.—I should like to ask just one question. I think that Dr. Sellards had the idea when he administered bicarbonate by mouth, that there were a certain number of individuals who had a definite diminution of the alkalis in their bodies as a whole with little change in the blood. In these it took a considerable amount of sodium bicarbonate by mouth to produce any effect on the urine, while the blood alkalinity showed relatively little change. In these cases he thought that the blood tended to reserve its alkali reserve at the expense of the tissues. What light does your method show on this?

DR. PALMER.—I had not mentioned this because of the introduction of too much mathematics into the paper. We found that if you calculate the body fluid on the basis of about 70 per cent water, you can calculate with a great degree of accuracy the effect the bicarbonate is going to have on the blood  $\text{CO}_2$ . We found no difference in the blood and the body fluid and the sodium bicarbonate was distributed with great rapidity and ease, so that I think that is not so.

DR. CLYDE GUTHRIE.—In addition to the effect of sodium bicarbonate already mentioned, I was under the impression that this substance might be retained in the body in various localities. A case in point is the reason for this question. A patient with a nephrosis had an intensive course of alkaline therapy, and I am uncertain whether at the time he had developed edema. Certainly following this therapy he developed it and likewise an ascites. Fluid was taken from his abdomen and found to be very strongly alkaline and the addition of dilute acetic acid made it effervesce in an extraordinary manner. It was my impression that the sodium bicarbonate was in this

instance retained in the body at a point perhaps outside of the circulation.

**DR. PALMER.**—I was responsible for this therapy and I think I should explain my part of the responsibility. He had been on the ward for some months, and was becoming impatient because he was not being treated. I have seen cases of this kind with edema, where acid urine was present. After changing the reaction of the urine, bringing it to neutral, diuresis occurred. This was tried on this man and he gained remarkable amounts of fluid. I don't believe it did the man very much harm.

#### 4. Contributions to Psychopharmacology. DR. D. I. MACHT.

To be published later.

## BIOGRAPHY OF SIR WILLIAM OSLER

Lady Osler has requested me to prepare a biography of her husband, and I will be most grateful to anyone who chances to see this note, for any letters or personal reminiscences, or for information concerning others who may possibly supply letters.

Copies of all letters, no matter how brief, are requested, and if dates are omitted it is hoped that they may be supplied if possible.

If the originals are forwarded for copy they will be promptly returned.

HARVEY CUSHING, M. D.,  
Peter Bent Brigham Hospital,  
Boston, Mass.

## PUBLICATIONS

The following eight monographs:

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## THE SIGNIFICANCE OF SYPHILIS IN PRENATAL CARE AND IN THE CAUSATION OF FOETAL DEATH<sup>1</sup>

By J. WHITRIDGE WILLIAMS

I think that it may safely be said that the propaganda for the development and extension of prenatal care, which has been conducted during the past few years in this country, constitutes one of the most important advances in practical obstetrics; as it has taught us to appreciate the unnecessary wastage of foetal life which has occurred in the past and to consider seriously how it may be diminished.

Unfortunately, this movement is not of medical origin, except in so far as the efforts of the pediatricians to popularize maternal suckling had led to some supervision over pregnant women. Years ago Budin instituted consultations for pregnant women in Paris, and Ballantyne of Edinburgh did important pioneer work concerning the production of foetal abnormalities and insisted upon the benefits which might follow intelligent antenatal care, yet real interest in the prophylactic supervision of pregnant women originated with laymen. Indeed, I do not think that I shall go far wrong when I state that the greatest credit in this respect belongs to Mrs. William Lowell Putnam, who some years ago organized at her own expense in Boston a small service in which women could be

supervised during the latter half of pregnancy for the purpose of instruction in the rudiments of the hygiene of pregnancy, of seeing that they were properly nourished and not overworked, of teaching the importance of suckling their children when born, and particularly of preventing the occurrence of eclampsia by the early recognition and treatment of the toxæmias of pregnancy.

One of the most important agencies in bringing about the reform in this country has been The Association for the Prevention of Infantile Mortality—now the American Child Hygiene Association; for at its meetings each year philanthropic laymen, social workers and trained nurses, as well as occasional medical men, read papers upon the subject and gradually aroused popular interest in it, and it was not until after the movement had attained considerable momentum that obstetricians became generally concerned with it, and even at present many of them still treat the subject in a luke-warm manner.

In its broadest sense, prenatal care may be defined as such supervision of the pregnant woman as will enable her to go through pregnancy safely, to bring forth a normal living child with minimal danger, and to be discharged in such good physical condition as to be able to care for her child

<sup>1</sup> Read before the Section on Obstetrics and Gynecology of the Medical Society of the state of New York, March 25, 1920.

efficiently and to suckle it for at least the first months of its life. This means that the women must be under medical supervision from the earliest possible period of pregnancy, so its various abnormalities may be recognized at their inception and treated prophylactically. It also means the application of the best methods of obstetrical diagnosis during the weeks immediately preceding labor, so that abnormal presentations, disproportion due to contracted pelvis, as well as other complications may be recognized, and corrected if possible before its onset. It further means the proper conduct of labor, and such supervision during the weeks immediately following it, that the woman may be discharged in such physical condition as to be able to carry on her usual avocations efficiently, and to give her child the necessary care. Finally, it implies medical supervision of the child during the first year of life, so that the effort expended during pregnancy and at the time of labor be not wasted; as it should be realized that the object of pregnancy is to secure a child which will have a reasonable prospect of reaching adult life, and that every preventable foetal or infantile death means biological and economic waste.

It is evident that such a program requires not only first-rate obstetrical care, but such supervision of the patient before and after delivery by trained nurses and social workers as will make it possible for her to realize the importance of following closely the various regulations laid down for her guidance. In other words, efficient prenatal care must be regarded in great part as a campaign of education for physician and patient, in which both must be taught to realize that ideal obstetrics implies not merely intelligent care at the time of labor, but that it has a much wider scope and should begin as soon as the woman realizes that she is pregnant and continue until she is discharged in ideal physical condition and suckling a normal child. As the majority of hospital patients belong to the less intelligent classes, it is only by means of education through prenatal workers that they can be induced to make the necessary visits to the dispensary before and after delivery, and consequently I have become convinced that efficient prenatal and postnatal care cannot be carried out by physicians alone, and is feasible only when the requisite number of trained nurses and social workers are available.

In the earlier work, attention was principally concentrated upon three points: (1) The recognition and earliest possible treatment of the toxæmias of pregnancy in the hope of preventing the development of eclampsia; (2) supervision of the general physical and material condition of the patient with the object of diminishing the chances of premature labor; and (3) such instruction during the latter part of pregnancy that the mother will be prepared to suckle her child after it is born. When, however, the subject was taken up by obstetricians, it became apparent that the best results could not be obtained unless the scope of the work were materially widened so as to include everything which is implied by good obstetrics, plus the supervision and instruction derived from nurses and social workers.

Soon after taking up this work, I realized that the recognition and treatment of syphilis early in pregnancy constituted an important and fruitful field for a radical reduction in fetal mortality, and in my presidential address—"Upon the Limitations and Possibilities of Prenatal Care"—before the American Association for the Prevention of Infantile Mortality in 1915, I developed the idea that more lives could be saved along such lines than by any other single method. That address was based upon the critical study of 700 foetal deaths occurring in 10,000 consecutive deliveries in the Obstetrical Service of The Johns Hopkins Hospital, and included not merely the deaths at the time of labor, but also those occurring during the last ten or twelve weeks of pregnancy, as well as those during the two weeks immediately following delivery. Upon analyzing the causes of death, it was found that syphilis was responsible for 26 per cent of the entire number, and that it caused more deaths than any other single factor, and very many more than the toxæmias of pregnancy, which up to that time had been considered the greatest field for prophylactic effort. Consequently, I concluded that if syphilis could be eliminated from among the causes of foetal death, greater progress in prenatal care would be made than by any other means at present available.

In the 700 cases under consideration the diagnosis was made by the recognition of congenital syphilis in the living child, or from the presence of certain histological changes in the placenta which we had learned to associate with the disease, while in only a relatively small proportion of the cases was it made at autopsy. With the discovery of the Wassermann reaction and the demonstration that the spirochete is the cause of syphilis, our knowledge concerning the disease became greatly widened, so that we were able to diagnose it in many mothers and infants in whom it had formerly been overlooked, as well as to demonstrate the syphilitic nature of certain lesions which had previously not been considered as having any relation with that disease.

While preparing my article in 1915, I became convinced that the only way in which the problem could be approached with any hope of effective solution was by determining the Wassermann reaction in every pregnant woman who registered in the Dispensary, and subjecting her to intensive anti-syphilitic treatment whenever it was positive.

This work was begun in April, 1916, and the present paper is based upon the critical study of 302 foetal deaths occurring in 4000 consecutive deliveries between that period and December 31, 1919. In this series every effort was made to elicit a possible history of syphilitic infection and to detect the presence of the clinical signs of the disease; moreover, a Wassermann test was made at the first visit of the patient, and, if a positive result were obtained, she was subjected to proper treatment in the Syphilis Clinic, provided sufficient time was available before delivery. At the conclusion of labor a Wassermann was likewise taken from the foetal blood obtained from the maternal end of the umbilical cord. Every placenta was preserved and examined histologically, and finally, if the child was born dead or died after delivery, every effort was

made to obtain an autopsy in order to determine accurately the cause of death, particular attention being given to the recognition of syphilitic lesions and to the demonstration of the presence of spirochetes. Consequently, in each of these 4000 cases we have a careful clinical history of the patient, as well as a record of the maternal Wassermann, of the foetal Wassermann at the time of birth, of the microscopical examination of the placenta, and in case of death of the child a complete autopsy, so that it is apparent that few cases of syphilis could escape recognition. Furthermore, all patients who presented a positive Wassermann were followed up by our social workers, and every effort was made to see that they were appropriately treated. At present we are endeavoring to get back as many patients as possible, who at any time presented signs of syphilis, for the purpose of ascertaining what has happened to them and their children. Unfortunately, however, this information will not be available for incorporation into this paper, which is based more particularly upon the critical study of the foetal deaths occurring in this series of cases, while the conclusions to be drawn from the Wassermann reaction will be considered in a report to be made to the American Gynecological Society in May.

I think it only fair to preface our study by saying that our material differs from that which may be collected in many other cities by the fact that somewhat more than one-half of our patients were blacks. Thus, in the 4000 cases under consideration, there were 1839 white and 2161 black women, in whom a positive Wassermann reaction was present in 2.48 and 16.29 per cent, respectively. In other words once in every fortieth white, and once in every sixth colored woman. It should, however, be borne in mind that this incidence does not exhaust the possibilities of syphilis, as there were 105 additional women in the series in whom the Wassermann reaction was negative, but in whose histories some mention was made of syphilis. Forty-four of these had presented a positive Wassermann in a previous pregnancy, which had later become negative following efficient treatment, with the result that the present pregnancy ended in the birth of a normal child. On the other hand, in the remaining 61 women, autopsy revealed characteristic lesions and the presence of spirochetes in the foetal tissues, or the live child presented clinical evidence of hereditary syphilis, or the placenta showed characteristic histological lesions.

Of the 302 dead babies 212 came to autopsy. In the former are included not only those dying at the time of labor or during the two weeks immediately following it, but also those dying during pregnancy from the time of viability onward: namely, children weighing between 1500 and 2500 grammes or measuring between 35 and 45 cm. in length. Of the 302 deaths, 99 occurred in white and 203 in black infants, an incidence of 5.4 and 9.4 per cent, respectively; while 157 occurred at the time of labor or during the first two weeks of the puerperium, and 145 were in premature children.

Syphilis was noted in 104 cases, in 89 of which the diagnosis was confirmed by autopsy with the demonstration of spirochetes in the foetal tissues; while in the remainder it was

made from the presence of syphilitic lesions in the placenta, associated with a positive Wassermann on the part of the mother. Upon analyzing the causes of death, we obtained the following figures:

	Cases	Percentage
Syphilis .....	104	34.44
Dystocia .....	46	15.20
Toxæmia .....	35	11.55
Prematurity .....	32	10.59
Cause unknown .....	26	8.61
Placenta prævia and premature separation .....	16	5.28
Deformity .....	11	3.64
Eleven other causes .....	32	10.69
	302	100.00

Before considering these figures critically, it may be well to say a few words as to how the classification was established, it being understood that the cause of death was determined partly from the autopsy findings and partly from careful study of the clinical history of each case. Thus, in 89 of the 104 syphilitic cases, the cause of death was determined by autopsy, while in the remaining 15 it was based upon clinical findings in the child, or upon the presence of syphilitic lesions in the placenta associated with a positive maternal Wassermann.

Under dystocia are included all deaths resulting from mechanical difficulty or undue delay at the time of labor; as for example, craniotomy, decapitation, birth injuries following operative delivery, prolapse of the cord, undue delay during the second stage incident to disproportion between the size of the child and the pelvis, etc. A certain proportion of such deaths must be attributed to error in judgment on the part of those conducting the delivery, while others were unavoidable. Under the deaths attributed to toxæmia are included not only the children which were born dead during an eclamptic attack, but also the premature live children, which were born spontaneously, or as the result of the induction of labor, and could not be raised.

In the category of prematurity, we have included only children whose imperfect state of development appeared to be the sole cause of death. In such cases, no lesions were found at autopsy, and the children appeared to be normal except for their small size. Of course it is possible that a more intensive search for spirochetes might have led to a positive result in a certain number of these cases, particularly when the maternal Wassermann was positive, but, as they were not found, the cause of death was set down as prematurity. Moreover, it should be understood that we have not included in this category premature children born of mothers suffering from toxæmia, placenta prævia or acute infectious diseases, etc., as under such circumstances death was attributed to the underlying disease, and not to the imperfect development of the child.

Great interest attaches to the 26 cases for which no cause of death could be ascertained. In none of the 14 babies included in this group which came to autopsy could definite

lesions be demonstrated; while in the other 12 careful study of the clinical course of labor did not enable us to formulate a satisfactory explanation for the fatal outcome. In several of the autopsy cases, syphilitic lesions could not be demonstrated in the foetal organs nor spirochetes be found, despite the fact that the mothers presented a positive Wassermann or the placenta showed specific changes, so that death could not be attributed to syphilis, no matter what the presumption might be. This group of deaths is of great interest as it affords striking evidence of how little we really know of antenatal pathology, and suggests important possibilities for future research.

It is not necessary to consider in any detail the deaths associated with *placenta prævia* or with premature separation of the normally implanted placenta, as they are clearly the result of the underlying abnormality. Likewise, in the category of deformity, which includes examples of hydrocephalus, anencephalus, *spina bifida*, atresia of the intestinal tract, developmental abnormalities of the heart, etc., the condition originated in the earliest periods of embryonic life, and could not have been prevented by any means at our disposal.

Finally, in the last group are collected 32 deaths, which were attributable to one of eleven different causes, including atelectasis, about which we know nothing, acute infectious diseases of the mother, accidental suffocation, foetal bacteraemia, haemorrhagic disease, etc. Many of these were clearly unpreventable, while in others our knowledge concerning the underlying cause is so hazy as to make any positive statement inadvisable.

Upon analyzing the figures in the summary given above, it is seen that 89.3 per cent of the deaths are attributable to seven groups of causes, of which syphilis is the most important, as it accounts for 34.44 per cent of the total number, which is almost as high as the mortality for the next three groups combined, as dystocia, toxæmia and prematurity were responsible for 37.34 per cent, or only 3 per cent more than syphilis. Consequently, it is apparent that if we were possible to eradicate syphilis from our material, we should effect as great a reduction in foetal mortality as by doing away with all foetal deaths due to the various accidents at the time of labor, toxæmia, and prematurity combined. This, however, is manifestly out of the question.

As large as these figures seem, they do not entirely represent the ravages of syphilis, since we have already pointed out that it is quite possible that more careful search might have revealed the presence of spirochetes in the tissues of a considerable fraction of the autopsies in which the cause of death was attributed to prematurity, as well as in a certain number included in the unknown group. Moreover, these figures do not include the cases of congenital syphilis which appeared in babies which were discharged alive, or in whom the disease developed later.

It must be admitted that this unusually large incidence of syphilis can only apply to hospital services with a large black clientele, such as ours, and will not be noted in private practice or in hospitals in communities in which the majority of

the inhabitants are white, or in which the colored people are more intelligent than here. Nevertheless, even if we consider only our white patients, syphilis still continues to be a very important cause of foetal death, and this we know by experience can be in great part eliminated. As was indicated above, there were 99 white and 203 black infant deaths in our material, and in them syphilis was the etiological factor in 12.12 and 45.23 per cent, respectively. In other words, one out of every eight of our white babies died from syphilis as compared with every other black baby.

Upon comparing this 12 per cent mortality from syphilis in white infants with the other causes of death, it is seen that it exceeds all other causes except dystocia, and is nearly as great as for that. In other words, while 15.2 per cent of our children died from the various accidents of labor, 12.12 per cent of the white children died from syphilis, so that it is apparent that even in the white race syphilis represents one of the most important causes of foetal death, and is responsible for a greater mortality than toxæmia. Consequently, we should avail ourselves of every method to recognize its existence as early as possible, and then to treat it energetically.

This means that all obstetrical patients should be encouraged to register not later than the third or fourth month of pregnancy, that a routine Wassermann should be made at the first visit, and in case the result is positive, intensive treatment should be started immediately. In the case of the ignorant patient, mere advice to return at stated dates for treatment will not suffice, and it will be necessary for the social worker to follow her to her home and insist upon the necessity of following all directions implicitly. This frequently requires numerous visits, but only in this way can ideal results be obtained. Of course this means the expenditure of a large amount of time on the part of the workers, as well as a considerable financial outlay.

I had hoped to be able to give figures showing a marked contrast between the results obtained in the past when the Wassermann was made only when indicated by the history of the patient and those obtained in the present series in which it constituted a routine procedure. Unfortunately, so many elements enter into such a comparison that the tabulations are not convincing, but the following figures will give a graphic idea of what may be accomplished. Of the 4000 women under consideration, 421 presented a positive Wassermann reaction, but unfortunately all of them did not receive ideal treatment. In many instances they registered too late to receive any treatment, while others returned so irregularly that they were imperfectly treated, as for some time we had too few prenatal workers to supervise the patients efficiently, with the result that only a relatively small proportion received ideal treatment. With this in mind, we have divided the 421 patients into three groups, namely:

- a. No treatment.
- b. Inefficient treatment. The patients who received only two or three injections of salvarsan and no after treatment.
- c. Satisfactory treatment. The patients received from four to six injections of salvarsan followed by a course of mer-

curial treatment, with the result that the Wassermann became negative and remained so.

In the three categories there were 157, 103, and 163 patients, respectively, and the results of treatment are graphically showed by the fact that in group *a* 52 per cent of the children were born dead or presented some evidence of syphilis, as compared with 37 per cent in group *b*, and only 7.4 per cent in group *c*. In other words, the evidence at our disposal shows that if syphilis is recognized early in the pregnant woman, and is intensively and appropriately treated, almost ideal results may be obtained so far as the child is concerned. Consequently, there is every reason to hope that in the future syphilis may be practically eradicated as the cause of foetal death in all properly conducted clinics in which the women register prior to the middle of pregnancy.

On the other hand, it must be realized that even with the most perfect mechanism, ideal results will never be obtained, inasmuch as our investigations show that the disease will escape recognition in a certain proportion of pregnant women for the reason that the women frequently exhibit no clinical manifestations and occasionally present a negative Wassermann as well, so that the existence of the disease is not suspected until a macerated child is born and is shown to be syphilitic at autopsy. This, however, should not discourage us, for such occurrences are comparatively rare, and if the

course of procedure here outlined is faithfully followed, syphilis can be reduced from the most important cause of foetal death to one of the least frequent.

I hope that you will not think I have been one-sided in presenting the subject as I have, or that my judgment has been warped by our experience in Baltimore. I am well aware that syphilis represents only one of the causes of foetal death, and that all the others must be taken into consideration in a broad program for the reduction of foetal mortality, but at the present time syphilis appears to offer the most promising field for immediate results. A little thought will make it clear that a considerable proportion of the deaths from dystocia are unavoidable, and until our knowledge concerning the mode of production of eclampsia has become further extended, we must consider that its prophylaxis has almost reached its limit. Likewise, there is no immediate prospect of reducing the mortality from prematurity, as we are almost entirely ignorant concerning the causation of spontaneous premature termination of pregnancy, except when syphilis, toxæmia or gross over-exertion is the underlying factor. Moreover, it must be acknowledged that the foetal death-rate associated with placenta prævia and premature separation of the placenta is susceptible of only very gradual improvement while that due to congenital deformity is at present altogether beyond our control.

## TRANSIENT AND PAROXYSMAL AURICULAR FIBRILLATION

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This paper will deal with the instances of transient and paroxysmal atrial fibrillation encountered at The Johns Hopkins Hospital since auricular fibrillation was first recognized. It does not include the instances of auricular flutter in which auricular fibrillation is often present for a variable length of time before the establishment of a normal rhythm, nor with the period of transition from a normal rhythm to permanent atrial fibrillation in mitral and other valve lesions and in cases of chronic myocarditis, unless this period occupied a considerable length of time.

The mechanism of atrial fibrillation was first suggested by Cushny<sup>1</sup> in 1899 and more definitely formulated by Cushny and Edmunds<sup>2</sup> a few years later. The work of Mackenzie,<sup>3</sup> Hering,<sup>4</sup> Lewis<sup>5</sup> and Rothberger and Winterberger<sup>6</sup> was, however, of fundamental importance. By means of polygraphic and electrocardiographic methods and animal experimentation, they were able to prove that Cushny's surmise was correct and to demonstrate the relative frequency and great importance of this arrhythmia in clinical medicine.

It is of interest that the patient, whose case was studied by Cushny and Edmunds<sup>2</sup> was subject to attacks of tachycardia with complete irregularity of the radial pulse over a long period of time and that this is probably the first instance

of paroxysmal auricular fibrillation to be found in the literature.

Since then the recorded cases have increased somewhat in number, although no careful study of the condition has been made except by Krumbhaar<sup>7</sup> and by Heitz.<sup>8</sup> A number of other observers have reported a few isolated examples. Many of the reports, however, are incomplete, and in not a few lack of electrocardiographs or adequate polygraphic tracings makes it impossible to be certain of the exact nature of the arrhythmia.

It will be advantageous to summarize briefly some of the previous reports in an attempt to bring together certain evidence that has some bearing on the conclusions to be made below.

Hornung<sup>9</sup> in 1907 reported three instances of paroxysms of tachycardia with irregular radial rhythm in patients with hypertension and signs of myocardial insufficiency. Only radial pulse tracings are shown, but there can be little doubt but that he was dealing with arrhythmias dependent on paroxysms of auricular fibrillation.

A year later Hewlett<sup>10</sup> reported the case of a patient whom he had observed during eight paroxysms of atrial fibrillation. The patient was the subject of severe heart disease dependent on mitral stenosis.

Lewis<sup>12</sup> observed an instance of paroxysmal tachycardia in which the auricles fibrillated for about half a minute during one paroxysm. This patient had no obvious myocardial weakness. Four other cases are very briefly mentioned by him in a later report.<sup>5</sup>

Fox<sup>13</sup> reported the cases of Cushing and Edmunds<sup>2</sup> and Hewlett<sup>14</sup> and added two other cases. One patient was the subject of myocardial insufficiency in whom the irregularity later became permanently established; the other, a patient supposedly free from myocardial disease, developed a transient attack of atrial fibrillation following ether anaesthesia and a surgical operation.

Lewis and Schleiter<sup>14</sup> reported an interesting case of paroxysmal auricular fibrillation which they had observed for several months. During that time there were five paroxysms of atrial fibrillation, one of regular tachycardia and one attack in which both occurred. The patient had a mitral valve lesion and evidence of myocardial weakness. In another patient, an elderly man with arteriosclerosis and myocardial insufficiency, they observed many attacks of regular tachycardia and one attack of auricular fibrillation.

Heitz,<sup>15</sup> in a very complete article on the subject, reported 10 instances of paroxysmal auricular fibrillation. This group consisted mainly of elderly patients with hypertension and arteriosclerosis and consequent myocardial weakness. A few were the subjects of heart disease dependent on valvular lesions.

Robinson<sup>16, 17</sup> observed transient atrial fibrillation in a supposedly healthy man following hydrogen sulphide poisoning. The patient recovered completely. In another instance attacks of fibrillation occurred in a patient with cardiac hypertrophy, arteriosclerosis, and evidences of heart failure.

Fahrenkamp<sup>18, 19</sup> observed transient auricular fibrillation in the course of Basedow's disease, of pneumonia, and of fatal septicæmia, and also in a patient with myocardial weakness dependent on arteriosclerosis.

Cohn,<sup>20</sup> in a study of the behavior of the heart in 123 cases of acute lobar pneumonia, encountered 12 instances of transient auricular fibrillation.

Krumbhaar<sup>21</sup> observed transient atrial fibrillation, in the course of lobar pneumonia, in a patient with slight myocardial disease; also in a young man suffering from fatal cardiac decompensation during the course of a pericarditis and mitral valve disease.

Levine<sup>22</sup> in a series of 128 consecutive cases of atrial fibrillation at the Peter Bent Brigham Hospital found that in 14.1 per cent the arrhythmia was transient or paroxysmal. Details of these cases are not given. The series includes four cases of auricular flutter, two of acute rheumatic fever, three of chronic myocarditis and one each of pneumonia, hyperthyroidism, cancer of the oesophagus, chronic alcoholism and chronic valvular disease. In four other cases he thought the attacks followed active digitalis therapy and in one the condition followed a surgical operation under ether anaesthesia.

Weiser<sup>23</sup> reported the case of a patient with extensive endocarditic lesions in whom attacks of fibrillation had occurred.

There are probably more cases recorded in the literature, although a careful search has been made. Enough have been cited, however, to show, in general, the type of case in which the arrhythmia has been observed most frequently, as well as some of the rarer conditions under which it has been encountered.

*Incidence.*—The 18 cases which form the basis of this report were found among the hospital records of 258 medical admissions, classified under the heading "Auricular Fibrillation." Without deducting readmissions, in about 7 per cent of the total number of cases of auricular fibrillation the arrhythmia was transient or paroxysmal. This percentage is probably too low, for in some instances an arrhythmia which occurred for a few hours was not carefully analyzed; in other instances, even though the arrhythmia was due to fibrillation, it was not so classified among the hospital records.

This figure, however, agrees very closely with Krumbhaar's<sup>24</sup> statistics, but is considerably lower than the 14 per cent reported by Levine,<sup>22</sup> although the fact that he included several cases of auricular flutter in his series partly accounts for the higher percentage. Fahrenkamp's<sup>18</sup> figures are much smaller. In his opinion transient or paroxysmal atrial fibrillation is a very rare condition which is often confused with extrasystolic irregularities.

There are, however, enough well-studied cases in this series to prove that fleeting attacks of auricular fibrillation are not uncommon; indeed, it is probable that many of the attacks of palpitation and breathlessness of which elderly patients complain are due really to paroxysmal atrial fibrillation.

*Definition of Terms.*—The terms "paroxysmal" and "transient," as applied to auricular fibrillation, have been used synonymously in the literature, except by Krumbhaar.<sup>21</sup> He drew attention to a group of cases in which the attacks of fibrillation may be truly characterized as "paroxysmal" and some further proof of this assumption will be brought forward in this paper.

Auricular fibrillation, once it makes its appearance, is usually permanent. There are a few patients, however, in whom the transition from normal rhythm to permanent auricular fibrillation may not be abrupt, but may extend over several months. In such instances, attacks of fibrillation alternate with a normal cardiac rhythm throughout the transition period.

Many of the reported instances of transient and paroxysmal auricular fibrillation have occurred in patients in whom this transition period, for reasons that we do not understand, has been unduly prolonged, and it is possible that in every instance the arrhythmia would have become permanent had the patient lived long enough or been observed over a sufficient period of time.

Such reasoning, however, is largely a question of terms and does not disprove the assumption that there is a group of cases, clinically very similar and true to type, in which the arrhythmia, presumably due to auricular fibrillation, may occur in paroxysms throughout a period of 10 or even 20 years, and in which no evidence of a tendency of the arrhyth-



FIG. 1.—Case 14. L<sub>p</sub>. Jan. 22, 1919.  
Normal mechanism with sinus tachycardia.



FIG. 2.—Case 14. L<sub>p</sub>. Feb. 6, 1919.  
Atrial fibrillation alternating with paroxysmal tachycardia.

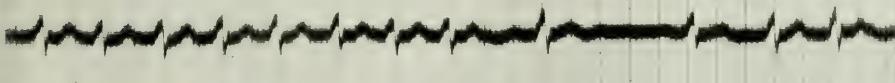


FIG. 3.—Case 14. L<sub>p</sub>. Feb. 6, 1919.  
Paroxysmal tachycardia.



FIG. 4.—Case 16. L<sub>n</sub>. June 19, 1919.  
Paroxysmal auricular fibrillation.

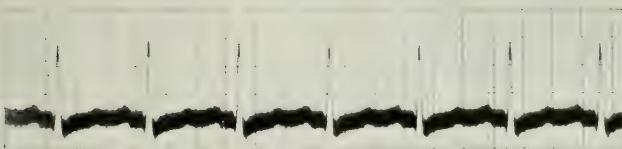


FIG. 5.—Case 16. L<sub>n</sub>. June 20, 1919.  
Normal mechanism.



FIG. 6.—Case 11. L<sub>p</sub>. Nov. 18, 1918.  
Auricular fibrillation.

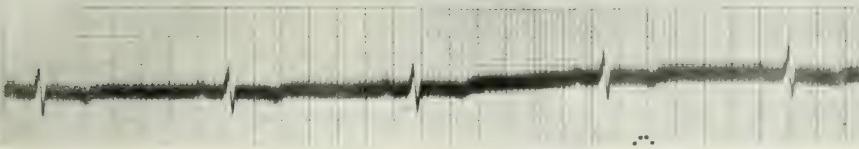


FIG. 7.—Case 11. L<sub>p</sub>. Nov. 26, 1918.  
Slight sinus arrhythmia. Spaced "p" waves present.



FIG. 8.—Case 13. L<sub>2</sub>. Jan. 28, 1919.  
Normal mechanism.

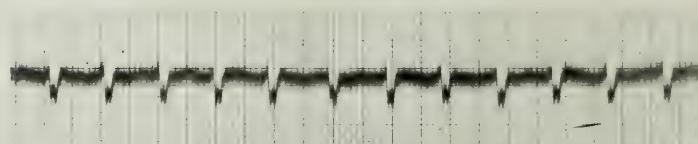


FIG. 9.—Case 13. L<sub>2</sub>. Jan. 30, 1919.  
Paroxysmal tachycardia.



FIG. 10.—Case 13. L<sub>2</sub>. Jan. 31, 1919.  
Paroxysmal tachycardia alternating with atrial fibrillation.



FIG. 11.—Case 12. L<sub>2</sub>. Nov. 9, 1918  
Complete A. V. dissociation due to digitalis.



FIG. 12.—Case 12. L<sub>2</sub>. Nov. 13, 1918.  
Atrial fibrillation.

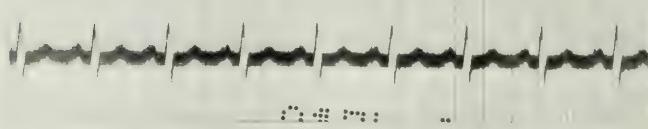


FIG. 13.—Case 12. L<sub>2</sub>. Nov. 20, 1918.  
Normal mechanism.



FIG. 14.—Case 12. L<sub>2</sub>. Jan. 22, 1919.  
Normal mechanism.

mia to become established permanently is present during the life of the patient or during the period of observation.

These instances present the picture of true paroxysmal auricular fibrillation, even though permanent auricular fibrillation occasionally occurs during the end stage, when symptoms of grave myocardial insufficiency present themselves. A full discussion of this clinical syndrome will be found below.

Transient auricular fibrillation is a much rarer condition. It has been observed most frequently during the course of acute intoxications and infections, and is caused by the action of such poisons on some part of the cardiac mechanism.

*Association with Other Arrhythmias.*—It is of interest that paroxysms of auricular fibrillation, of short duration, have been observed by Lewis<sup>2</sup> and by Lewis and Schleiter<sup>3</sup>

TABLE I

Case No.	Age	Size of heart	Symptoms of heart disease	Primary condition
1	66	Enlarged .....	Marked .....	Arteriosclerosis.
2	37	Enlarged .....	Marked .....	Mitral valve disease.
3	56	Enlarged .....	None .....	Exophthalmic goitre.
4	38	Enlarged .....	Marked .....	Arteriosclerosis. Hypertension.
5	61	Enlarged .....	None .....	Malignant endocarditis.
6	60	Enlarged .....	Slight .....	Chronic myocarditis.
7	52	Enlarged .....	Doubtful .....	Bronchopneumonia, mild. Chronic myocarditis.
8	66	Enlarged .....	Severe .....	Hypertension. Arteriosclerosis.
9	50	?	?	Bronchiectasis. Pleural effusion.
10	56	Enlarged .....	Marked .....	Aortic insufficiency. Arteriosclerosis.
11	67	Enlarged .....	Moderate .....	Hypertension.
12	32	Enlarged .....	Marked .....	Valvular disease.
13	42	Enlarged .....	Severe .....	Luetic pulmonary arteritis. Arteriosclerosis.
14	39	Enlarged .....	Severe .....	Acute and chronic endocarditis.
15	68	Normal .....	None .....	Hypertension. Carcinoma of esophagus.
16	50	Normal .....	Slight .....	Hypertension.
17	55	Enlarged .....	Marked .....	Chronic nephritis. Hypertension.
18	58	Normal .....	Slight .....	Chronic myocarditis.

during the course of paroxysmal tachycardia of auricular origin. The relation of the two disturbances to each other is not clear. Both, however, are associated with abnormal auricular activity (see Figs. 10 and 2).

In one case observed by us (J. H. H.) paroxysms of regular tachycardia preceded paroxysms of auricular fibrillation (the electrocardiograms did not show auricular flutter). Eventually auricular fibrillation became permanent.

Falconer and Dean<sup>2</sup> and Schwartzmann<sup>2</sup> observed paroxysms of auricular fibrillation in patients with heart-block. Such instances are very rare and are probably purely coincidental.

Auricular flutter with paroxysms of auricular fibrillation has been observed frequently. Indeed, it is the rule for auricular flutter to be followed by auricular fibrillation for a longer or shorter interval before the inception of a normal rhythm.

*Etiology.*—Table I shows the age, the presence or absence of cardiac enlargement and cardiac symptoms and the probable etiological factors in the cases summarized below.

It is evident that over two-thirds of the patients were in the sixth decade and this has been true of most of the reported cases. The exceptions have occurred most frequently either in patients with severe endocardial lesions in whom the arrhythmia was dependent on a rapidly failing myocardium, or during the course of a pneumonia, sepsis or other acute intoxication.

The primary condition, of which auricular fibrillation, whether permanent, transient or paroxysmal, is a clinical sign, is not fully known at present. It is justifiable, however, to assume that in the great majority of instances myocardial lesions are present, although it is not impossible that the arrhythmia, in some cases, may be dependent on extracardiac factors. Gossage and Hicks<sup>2</sup> and Levine<sup>10</sup> have suggested that fibrillation may occur occasionally in normal hearts, and Robinson,<sup>11</sup> in a heart carefully studied after death, found no lesion to account for the arrhythmia.

In this series of cases, cardiac disease, as evidenced by symptoms of myocardial weakness with or without cardiac enlargement, has been a nearly constant finding as will be seen in Table I. In a few instances, in which the only evidence of cardiac disease was an attack of auricular fibrillation, it has been necessary to assume that cardiac changes due to arteriosclerosis or hypertensive vascular disease were present.

Transient auricular fibrillation has been observed but rarely among our cases. In two instances, Cases 5 and 9, acute infections precipitated the attacks. In Case 3 hyperthyroidism of long duration was present and had probably led to permanent cardiac damage.

We may group these 18 cases as follows:

A. Myocardial weakness due to hypertension, arteriosclerosis, chronic valvular lesions or unknown factors (Cases 1, 2, 4, 6, 7, 8, 10, 11, 12, 13, 14, 15, 17, 18).

B. Acute infections or intoxications (Cases 3 (?), 5, 9).

The cases of true paroxysmal auricular fibrillation are found in Group A; of transient auricular fibrillation in Group B.

*Clinical Considerations.*—There is a large group of cases presenting a fairly typical and uniform clinical picture in which the attacks of auricular fibrillation, recurring at intervals throughout many years, are the most striking clinical findings.

The patient is usually an elderly individual, whose symptoms consist of breathlessness and palpitation occurring in paroxysms, either during physical exertion, mental strain or at times even during sleep. Between the attacks there are relatively few symptoms referable to the cardiovascular system, although usually any unaccustomed exertion is followed by slight dyspnoea.

The patient seeks advice of a physician either on account of the "heart attacks" or because of increased breathlessness on exertion. Physical examination usually reveals the presence of increased cardiac dulness, some peripheral arteriosclerosis and occasionally hypertension. Subsidiary findings,

such as chronic bronchitis and emphysema or a mild grade of renal disease, may be present.

Electrocardiographic studies show a normal sequence except during an attack when either a coarse or fine type of auricular fibrillation is present.

Cases 1, 6, 10, 15, 16, 18 represent fairly typical instances of paroxysmal auricular fibrillation and demonstrate the similarity of symptomatology presented by this group of patients.

One is impressed by the fact that the clinical picture is that of mild or, of course, eventually, of more severe myocardial weakness in which the paroxysms of auricular fibrillation are prone to occur after any unusual demand on the heart.

Transient auricular fibrillation needs no special comment at this time. As stated previously, it is a rare condition due to the action of certain poisons on the heart-muscle, or perhaps on the nervous mechanism of the heart. The subject has been fully discussed by Robinson. Until the essential cause of auricular fibrillation is known the pathological condition necessary for its production will remain the subject of speculation.

A few patients with endocardial lesions have shown attacks of atrial fibrillation. In them the arrhythmia is one more sign of myocardial insufficiency and usually becomes permanent long before death. Such patients, in the majority of instances, are simply passing through a prolonged transition period.

**Prognosis.**—It is not possible to make any definite statement concerning prognosis until the essential cause of auricular fibrillation is known and the nature of the lesions which may lead to its inception is better understood.

A careful consideration of the instances of transient and paroxysmal fibrillation, however, demonstrates that, as a rule, there is either chronic progressive myocardial weakness or that the arrhythmia, in some unknown manner, is dependent on an intoxication or an infection.

In the latter instances complete recovery with resumption of normal rhythm often occurs.

The prognosis, in the group of cases to which the term paroxysmal fibrillation has been applied, depends on the extent and character of the underlying lesion.

In many instances very few signs and symptoms of myocardial disease are present, and in spite of frequent attacks of fibrillation such patients often live for many years, comparatively free from symptoms. In other instances, the myocardial disease may progress rapidly and lead to an early death.

Early operation in patients with hyperthyroidism and transient fibrillation might be followed by the resumption of normal rhythm, but as yet too few instances have been reported to permit definite statements.

**Summary.**—Eighteen cases of paroxysmal and transient auricular fibrillation are reported.

A certain proportion of these present a fairly typical clinical syndrome in which the attacks of auricular fibrillation are paroxysmal in character.

**CASE 1.—Summary:** Paroxysmal fibrillation in association with arteriosclerosis and progressive myocardial weakness.

J. H., Med. No. 32493, aged 66. **Diagnosis:** Arteriosclerosis. Chronic myocarditis.

During past six months there have been increasing weakness, shortness of breath and 40 pounds loss of weight. On admission on April 27, 1914, there were signs of heart failure: large heart, B. P. of 150 systolic. Arteriosclerosis. Pulse irregular in force and rhythm. April 28, E. K. showed paroxysmal auricular fibrillation.

By May 5 the pulse was regular and remained so until discharge on May 22, 1914.

**CASE 2.—Summary:** Transient auricular fibrillation in patient with severe cardiac disease following acute rheumatic fever and hyperthyroidism.

I. M., Med. No. 33625, aged 37. **Diagnosis:** Mitral stenosis and insufficiency. Adherent pericardium. Exophthalmic goitre.

The patient had had chorea at 12 and polyarthritis at 13 and 36. Since the last attack she had had dyspnea and palpitation on exertion. There had been some edema. On admission, January 21, 1915, she had a huge heart with mitral valve disease and suggestive signs of adherent pericardium. There were definite signs of hyperthyroidism.

January 22. Pulse absolutely irregular, confirmed by polygraphic tracings.

January 24. E. K. Shows L. V. extra systoles and normal "p" waves.

February 10. E. K. Atrial fibrillation.

February 17. E. K. Normal rhythm.

March 1. E. K. Auricular fibrillation, right and left ventricular extra systoles.

**CASE 3.—Summary:** Numerous attacks of auricular fibrillation over many years; associated with chronic myocarditis. No symptoms of heart disease. Exophthalmic goitre.

L. M. S., Med. No. 34040, aged 56. **Diagnosis:** Exophthalmic goitre. Tumor of lung.

For the past 20 years the patient has had attacks of palpitation with rapid pulse at varying intervals lasting a few hours. Last June (1914) during a six-hour attack, the pulse was 170. In March, 1915, there were three brief attacks. On admission, April 14, 1915, there were no cardiac symptoms. Wide retrosternal dulness. Cardiac dulness 15 by 3.5 cm. Huge goitre. Pulse regular in force and rhythm.

May 9, 1915. Attack of auricular fibrillation, confirmed by E. K. Duration 12 hours. Pulse rate 160-170 per minute.

May 11. Short attack.

June 1. Short attack.

**CASE 4.—Summary:** Transient atrial fibrillation in a patient with severe nephritis, hypertension and myocardial disease.

M. B., Med. No. 35228, aged 38. **Diagnosis:** Chronic nephritis. Hypertension. Myocardial insufficiency.

About two months before admission began to have nocturia, headache, shortness of breath and edema.

On admission on December 17, 1915, the patient was orthopneic with edema of the face and body. B. P. 165/85. Cardiac dulness 5 by 20 cm. Pulse regular. The urine showed a large amount of albumin.

At 9 p. m. the auricles began to fibrillate, but the pulse was regular the next day.

December 20, 1915. Another attack of auricular fibrillation, but the pulse was regular on December 23, 1915, and remained so until discharge on January 22, 1916.

CASE 5.—*Summary:* Transient auricular fibrillation during course of malignant endocarditis.

J. C. B., Med. No. 37218, aged 64. *Diagnosis:* Mitral insufficiency. Bacterial endocarditis.

For the past six months there have been fever and progressive weakness.

On admission there was anæmia and weakness. Signs of mitral insufficiency. Large heart. *Streptococcus viridans* in blood and fever. Pulse regular in force and rhythm. During stay in hospital there were two short attacks of auricular fibrillation accompanied by palpitation and dyspnoea. The patient died several months later—January, 1917.

CASE 6.—*Summary:* Attacks of atrial fibrillation associated with mild myocardial insufficiency.

A. E. S., Med. No. 38851, aged 60. *Diagnosis:* Chronic myocarditis.

For the past two years has had attacks of marked palpitation lasting a few hours.

On admission on November 21, 1917, the pulse was totally irregular. B. P. 140/90. Cardiac dulness 3.5 by 14 cm. No marked symptoms.

November 22. E. K. Atrial fibrillation.

November 26, 27. E. K. Normal rhythm.

Discharged on December 17, 1917. Rhythm regular.

CASE 7.—*Summary:* Attacks of fibrillation of the auricles during the course of an acute bronchopneumonia in a patient with signs of slight myocardial disease.

H. T. B., Med. No. 39438, aged 52. *Diagnosis:* Chronic myocarditis. Bronchopneumonia.

Present illness began with cough, fever and pain in right side February 17, 1918.

On admission on February 19, 1918, there were signs of a mild bronchopneumonia. Cardiac dulness measured 4.5 by 14.5 cm. B. P. 130/80. Pulse totally irregular. E. K. shows atrial fibrillation.

February 20, the rhythm was normal, but attacks of fibrillation occurred on February 21 and on March 30, 1918.

Patient discharged on April 8, 1918. Normal rhythm.

CASE 8.—*Summary:* Transient attacks of atrial fibrillation during course of fatal heart failure secondary to arteriosclerosis and hypertension.

S. D., Med. No. 40095, aged 66. *Diagnosis:* Hypertension. Chronic myocarditis.

About December, 1917, the patient began to have dyspnoea on exertion. There has been progressive weakness. Oedema of legs for the past week. Admitted on July 16, 1918, with marked orthopnoea and some oedema. Peripheral vessels sclerosed. B. P. 195/140. Cardiac dulness measures 5 by 12 cm. Radial pulse regular. On July 17 auricular fibrillation set in, but the heart's rhythm was normal two days later. On July 23 the presence of auricular fibrillation was again shown by electrocardiograms, but soon disappeared. From this time until death—August 2, 1918—the pulse was regular in rhythm and numerous E. K.'s showed normal rhythm. *Autopsy:* Generalized arteriosclerosis, and more especially of renal arterioles. Cardiac hypertrophy.

CASE 9.—*Summary:* Attack of atrial fibrillation in patient with chronic pulmonary disease and probably myocardial weakness.

C. A. S., Med. No. 40293, aged 50. *Diagnosis:* Bronchiectasis. Pleural effusion.

About 18 months before admission the patient developed a cough with abundant sputum.

On admission on August 4, 1918, the pulse was regular in force and rhythm. The cardiac dulness was 5 cm. to the left and obscured on the right by a large pleural effusion.

On August 25 auricular fibrillation set in, but had disappeared the next day.

CASE 10.—*Summary:* Transient attack of atrial fibrillation in a patient with chronic myocardial insufficiency and aortic insufficiency dependent on arteriosclerosis (?).

J. B., Med. No. 40331, aged 55. *Diagnosis:* Myocardial insufficiency. Aortic insufficiency.

Signs of myocardial weakness for four years. An invalid for the past six months.

On admission August 24, 1918, there were dyspnoea and oedema. Cardiac dulness 4 by 16 cm. Well-marked aortic insufficiency. Pulse 100. Heart's rhythm normal.

August 27, 1918. Atrial fibrillation was present.

September 11, 1918. The electrocardiogram showed a normal rhythm.

The patient left hospital much improved, the blood-pressure had fallen from 190/100 to 140/80.

CASE 11.—*Summary:* Transient atrial fibrillation associated with severe myocardial disease and hypertension.

M. M., Med. No. 40868, aged 67. (Figs. 6 and 7.) *Diagnosis:* Hypertension. Chronic myocarditis.

For 15 years there has been palpitation on exertion. In September, 1918, the pulse was absolutely irregular.

On admission on November 15, 1918, there were symptoms of heart failure. The radial pulse was totally irregular. The blood-pressure was elevated. Cardiac dulness 3.5 by 13.5 cm.

November 18, 1918. E. K. shows auricular fibrillation.

November 26, 1918. Pulse regular and remained so until discharge—November 30, 1918.

CASE 12.—*Summary:* Transient atrial fibrillation in association with myocardial failure dependent on rheumatic valve lesion.

F. C., Med. No. 41200, aged 32. *Diagnosis:* Mitral insufficiency. Syphilis.

The patient had acute rheumatic fever in 1913. For the past three years there have been progressive symptoms of heart failure.

On admission on November 7, 1918, there was moderate dyspnoea. Cardiac dulness measured 5 by 11 cm. Pulse regular in force and rhythm.

November 9, 1918. E. K. shows complete A. V. dissociation.

November 13, 1918. Atrial fibrillation.

November 18, 1918. Cardiac rhythm regular.

December 24, 1918. Short attack of auricular fibrillation.

December 25, 1918. Rhythm regular.

February 1, 1919. Discharged. Pulse regular.

CASE 13.—*Summary:* Frequent attacks of auricular fibrillation associated with fatal myocardial failure dependent on arteriosclerosis.

G. P., Med. No. 41201, aged 42. (Figs. 8, 9, 10.) *Diagnosis:* Syphilis. Chronic myocarditis.

About November, 1917, the patient was taken with dyspnoea, lasting a few minutes. Since this has had numerous attacks at varying intervals, never over a few minutes in duration. Since November, 1918, there have been increasing dyspnoea and oedema.

On admission January 27, 1919, there were marked dyspnoea and oedema. Cardiac dulness 5 by 13 cm. Peripheral vessels soft.

January 27, 1919. Pulse regular in force and rhythm. 108 per minute.

January 31, 1919. Many slight attacks of tachycardia.

February 1, 1919. Sudden death.

*Autopsy:* Arteriosclerosis. Luetic arteritis (pulmonary). Hypertrophied heart.

CASE 14.—*Summary:* Attack of auricular fibrillation in a patient with active endocarditis associated with extensive chronic endocarditic valve lesions. Death.

I. U., Med. No. 41232, aged 39. (Figs. 1, 2, 3.) *Diagnosis:* Aortic insufficiency.

Since October, 1916, precordial pain and dyspnoea have been practically constantly present.

On admission on January 21, 1919, the patient was very ill. There was moderate fever throughout the stay in the hospital. W. B. C. not increased. Some cough. Cardiac dulness 3 by 14 cm. Pulse 108 regular, collapsing. On February 5, 1919, auricular fibrillation appeared, but was absent on February 6. February 7, 1919. Sudden death.

*Autopsy:* Acute aortic endocarditis. Chronic aortic, mitral and tricuspid endocarditis. Thrombosis of middle branch of right pulmonary artery.

CASE 15.—*Summary:* Two attacks of auricular fibrillation in a patient without evident heart disease. Hypertension. Cancer of oesophagus.

T. L., Med. No. 41792, aged 68. *Diagnosis:* Carcinoma of oesophagus. Hypertension.

The patient gives history of oesophageal obstruction. Emaciated. On admission May 2, 1919, there was no evidence of cardiac disease, but the blood-pressure was 210/110. Pulse regular. On two successive Sundays the heart rate became rapid and there was a pulse deficit. Radial pulse irregular in force and rhythm.

CASE 16.—*Summary:* Short attack of paroxysmal fibrillation in a patient with hypertension and mild symptoms of myocardial weakness.

G. L. D., Med. No. 42125, aged 50. (Figs. 4 and 5.) *Diagnosis:* Hypertension. Chronic myocarditis. Obesity.

First admitted to the hospital in February, 1919, complaining of dizziness, precordial distress and some palpitation for the past three months. Pulse regular. Heart not enlarged. Blood-pressure elevated. On June 18, 1919, he felt his heart fluttering and entered the hospital. The findings were as before, except that the pulse was totally irregular and there was a pulse deficit. An E. K. taken at this time showed paroxysmal auricular fibrillation. The next day the pulse was regular and an E. K. showed a normal rhythm. January 1, 1920. Cardiac rhythm regular.

CASE 17.—*Summary:* Attack of transient auricular fibrillation in a patient, the subject of advanced renal and myocardial disease and hypertension.

I. L. D., Med. No. 42714, aged 55. *Diagnosis:* Chronic nephritis. Hypertension. Arteriosclerosis.

There have been dyspnoea and oedema of the ankles since November, 1918, gradually becoming worse. In April, 1919, the pulse was regular; heart enlarged; B. P. 155/55; phenolsulphonephthalein excretion 22 per cent in two hours; secondary anaemia; hyposthenuria.

On admission on September 22, 1919, there were marked dyspnoea and oedema. Cardiac dulness measured 5 by 14 cm. Pulse regular in force and rhythm, vessel walls thickened.

On October 3 the pulse became irregular and remained so until October 12, 1919. From that time on the cardiac rhythm was normal until discharge—November 14, 1919.

CASE 18.—*Summary:* Numerous paroxysms of auricular fibrillation during two years in an elderly woman with mild symptoms of myocardial weakness.

G. P., Med. No. 30821, aged 58. *Diagnosis:* Paroxysmal auricular fibrillation.

For two years patient has suffered from attacks of dyspnoea and palpitation, repeated at frequent intervals and lasting from a few hours to a few minutes. During two attacks the electrocardiograms showed auricular fibrillation and between the attacks perfectly normal sequence. Blood-pressure normal. The heart is not enlarged nor is there dyspnoea except on exertion. R. C. D. 3.5 by 7.5 cm.

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#### BIOGRAPHY OF SIR WILLIAM OSLER

Lady Osler has requested me to prepare a biography of her husband, and I will be most grateful to anyone who chances to see this note, for any letters or personal reminiscences, or for information concerning others who may possibly supply letters.

Copies of all letters, no matter how brief, are requested, and if dates are omitted it is hoped that they may be supplied if possible.

If the originals are forwarded for copy they will be promptly returned.

HARVEY CUSHING, M. D.,

Peter Bent Brigham Hospital,

Boston, Mass.





DR. FLORENCE RENA SABIN.

## PRESENTATION TO THE UNIVERSITY OF THE PORTRAIT OF DR. FLORENCE RENA SABIN<sup>1</sup>

Dr. Sabin graduated from the Medical School of this University in 1900. After serving for a year as an interne in the hospital, she joined the anatomical staff under Dr. Mall, and was subsequently promoted from one grade to another until in 1917 she was made professor of histology. She is the first woman to attain the rank of a full professor in this university.

In her services as a teacher she has taken part in the instruction of over a thousand students, most of them young men. It might have been supposed that some of these young men would have objected to being put under a woman teacher, since a majority of them came from men's colleges in which such a relationship was regarded with disfavor to say the least. As a matter of fact there was never the least indication of a reaction of this kind. From the beginning Dr. Sabin succeeded in winning the confidence and regard of her students both men and women. She has been a conspicuously able and successful teacher not only in the matter of imparting sound knowledge, but also in the more difficult art of discovering the gifted student and stimulating him to independent work beyond the established routine of the classroom or the text-book. In this respect she has added example to precept, for from the beginning of her connection with the staff of the Medical School she has been a productive investigator. Early in her career she published a remarkable research upon the lymphatic system. By means of an ingenious method skillfully applied she was able to discover the mode of origin and development of the lymphatic vessels of the body. This paper was awarded the \$1000 prize offered by the Naples Table Association "for the best scientific thesis written by a woman embodying new observations and new conclusions based on independent laboratory research." It has since received, I believe, a much greater reward in the universally favorable recognition accorded to it by all anatomical writers interested in this field. There followed a series of contributions bearing upon the same general subject and appearing in various scientific journals here and abroad. The results of this work have been so important as to connect Miss Sabin's name indissolubly with this topic in medical literature. Her own contributions as well as those made by other workers she has summed up and discussed in a notable lecture delivered in 1915 before the Harvey Society of New York. This is not an appropriate occasion for enumerating all the scientific publications made by Dr. Sabin, but I cannot refrain from noting that in her last paper, appearing in the Mall Memorial Volume, 1919, she has made a contribution to our knowledge of the origin and development of the blood and blood vessels which is as fortunate and significant as her work on the lymphatic system. The course of years and the increasing complexity of her duties have not diverted nor

<sup>1</sup> Remarks made at the Commemoration Day Exercises, February 23, 1920, by Dr. William H. Howell.

diminished her capacity for investigative work. These and other papers have established Dr. Sabin's reputation as a leading authority in her subject and have brought to her recognition and honors in the scientific world. Smith College, her Alma Mater, conferred upon her the honorary degree of Doctor of Science, and several institutions have attempted to attract her to posts in their faculties. One interesting call of this kind was to the Chair of Anatomy in the Woman's Medical College, London.

When I think of Miss Sabin's work in the Medical School it seems to me that she has been an ideal university professor. Successful in teaching, productive in research, conscientious and cooperative in all routine duties of an administrative character. Following the admonition of Pasteur she has chosen to dwell in the serene peace of the laboratory and library, and in this environment has given her time and best energies to the work belonging to her position. The professor who prefers to use his talents in the wider life outside the library and laboratory may become a useful citizen or even a public benefactor, but nevertheless he fails in his major duty to his university and his science—for none of us can successfully serve two masters.

To Dr. Sabin as a scientist we must give our admiration and respect, but those of us who have been brought into daily association with her know that to ability of a high order there is added a rare combination of good qualities which confer upon her a rich personality. Sane and fair in her judgments, modest and unassuming in her actions, loyal, helpful and unselfish, she has by contrast an emotional side easily aroused in defense of a cause or a friend and not incapable of transforming a calm scientist into a warm partisan. Some such human factor is essential to give color and timbre to the more sober professorial attributes if a sympathetic understanding is to be reached between teacher and student. I fancy that Dr. Sabin's impulsive sincerity has helped greatly to open the way to the hearts of her pupils and friends.

In offering this painting to the University, Mr. President, we, her colleagues, students and friends, feel that it will be a matter of especial interest in the history of the Medical School to have preserved a portrait of its first woman professor, one of its most distinguished graduates and one who has contributed so much of real worth to the building up of the School and to the establishment of its reputation as a center of medical research.

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# DETERMINATION OF THE ACIDITY OF GASTRIC CONTENTS

## I. DETERMINATION AND SIGNIFICANCE OF ACIDITY

By ALFRED T. SHOHL, Baltimore

(From the James Buchanan Brady Urological Institute of The Johns Hopkins Hospital)

In acidity, the gastric juice is unique among all the body fluids. The blood is practically neutral and is maintained so with great constancy. Milk and saliva are about three times, the average urine twenty times, and sweat a hundred times, as acid as the blood. Gastric juice is a million times more acid than the blood. This acidity, as has long been known, is due to the presence of free hydrochloric acid. Clinically, the amount of acid is determined in the gastric contents after a test meal. That there are variations in the acidity of such contents is evidenced by the absence of HCl in cancer of the stomach and the high acidity in gastric ulcer. The practical importance of the determination is beyond dispute.

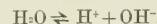
*Nature of Solutions.*—Since Prout, in 1824, showed that HCl was present in gastric contents and determined it quantitatively, and Szabo, in 1877, devised a method for titrating the HCl, our understanding of the nature of acidity has made great progress. Van't Hoff, in 1885, proved that substances dissolved in water behave like gases and follow the three gas laws: (1) Law of Boyle: The pressure increases proportionally as the volume decreases, for a given amount of gas; conversely, for a given volume of gas the pressure is proportional to the amount of gas present. (2) Law of Charles: For a given volume of gas the pressure increases as the absolute temperature. (3) Rule of Avogadro: All gases in amounts equal to their molecular weight, taken in grams, at equal temperature and pressure, occupy the same volume. In solutions one cannot, as in gases, measure the pressure directly, but it exists and is called osmotic pressure. It is a measure of the solution's capacity to draw water through a semi-permeable membrane. In terms of solutions, according to Van't Hoff, these laws become: (1) The osmotic pressure is proportional to the amount of substance present; (2) the osmotic pressure increases as the absolute temperature; (3) amounts of substances equivalent to their molecular weight, taken in grams, under similar conditions, exert the same osmotic pressure. Substances which increase osmotic pressure also raise the boiling point and lower the freezing point of solutions. The first and third laws of solutions may therefore be written: (1) The elevation of the boiling point or the depression of the freezing point is proportional to the amount of substance present; and (3) amounts of substances equivalent to their molecular weight, taken in grams, exert an equal effect on the elevation of the boiling point or on the depression of the freezing point.

*Electrolytes.*—Arrhenius, in 1887, showed that certain substances do not follow these laws exactly. Substances which act abnormally in solution—acids, bases and salts—he

grouped into one class, and because they and no others conduct electricity, he called them "electrolytes."

Acids, bases and salts show a greater osmotic pressure and greater effect on the boiling point and freezing point than do non-electrolytes. As an explanation of their action, Arrhenius then proposed the ionic theory. Electrolytes conduct electricity because each molecule dissociates or splits into two parts, called ions, which carry electric charges. These ions are called, respectively, the *anion* and *cation*. The anion carries the negative charge and the cation the positive. When electricity is passed through the solution, the anion, or negatively charged ion, goes to the positive pole and the cation, or positive, goes to the negative pole. Thus, if each molecule dissociates into two ions, there are twice as many parts in solution, and there is twice as great an effect on the osmotic pressure, the boiling point and the freezing point.

*Acids.*—Acids on dissociation always give hydrogen ions as the cations regardless of the kind of acid. Hydrochloric acid dissociates into H and Cl. One represents ionized hydrogen as  $H^+$  and ionized chlorine as  $Cl^-$ . Bases on dissociation always give hydroxyl ions as the anions, regardless of the kind of base. One represents hydroxyl ions as  $OH^-$ . A solution is acid when there are more  $H^+$  than  $OH^-$  in solution. A solution is alkaline when the  $OH^-$  are more numerous. If both are present in equal amount, the solution is neutral. Water itself dissociates into  $H^+$  and  $OH^-$  and partakes therefore of the nature of both acid and base. These ions are present in equal amount and so water is neutral. We may represent this in chemical notation as:



The equilibrium which has been expressed above means that water dissociates into its ions at the same speed at which the ions unite to form water. This is an example of the law of mass action: The speed of reaction is proportional to the concentration of the interacting substances. When equilibrium is established, the speed in either direction is the same. The amount of ions formed fixes the numerical value of the equilibrium, for the product of the hydrogen times the hydroxyl ions divided by the amount of undissociated water is a constant. The total number of ions present depends on the nature of water and is constant for any temperature. Representing the value of this constant by the symbol K and concentration by symbols in parenthesis, the chemical equation follows:

$$\frac{(H^+) \times (OH^-)}{(H_2O)} = K \quad (1)$$

or

$$(H^+) \times (OH^-) = K(H_2O); \quad (2)$$

or since the amount of water is so large in proportion to the number of ions, one may consider the amount of undissoiated water as unity and write the equation

$$(H^+) \times (OH^-) = K. \quad (3)$$

This constant of water has been measured accurately. At 20° C. its value is

$$10^{-14} \text{ or } .0000000000000001.$$

Since  $(H^+) = (OH^-)$  the equation may be written:

$$(H^+) \times (H^+) = 10^{-14}, \quad (4)$$

or

$$(H^+)^2 = 10^{-14}, \quad (5)$$

or

$$(H^+) = 10^{-7}. \quad (6)$$

*Expression of Acidity.*—In measuring the acidity of solutions, one measures the amount of hydrogen ions per liter or the hydrogen-ion concentration per liter. One expresses the hydrogen-ion concentration in terms of a fraction of a gram of hydrogen ions per liter. The hydrogen-ion concentration of pure neutral water is  $10^{-7}$ . A solution is acid when the  $(H^+)$  is greater than  $10^{-7}$ , or alkaline when the  $(H^+)$  is less than  $10^{-7}$ .

In one liter of normal HCl there is one gram of hydrogen, for normal solutions of monobasic acids contain the molecular weight of the substance taken in grams. Since the atomic weight of hydrogen is 1, all normal solutions of acid contain

calculated from a formula in which the negative logarithm of hydrogen-ion concentration is an essential part. This he writes with the symbol pH. It is the negative exponent of ten expressed as a positive number. By pH the hydrogen-ion concentration is characterized quite as well as if it were converted into the actual number, and is used even in the case of alkaline solutions. Thus, in tenth normal acid (assuming all the hydrogen to be ionized)  $(H^+) = .1$  or  $10^{-1}$  or pH 1.0. In hundredth

TABLE 2 \*

pH	Number	pH	Number
1.0	$1 \times 10^{-1}$	1.7	$2.0 \times 10^{-2}$
1.1	$7.9 \times 10^{-2}$	1.8	$1.6 \times 10^{-2}$
1.2	$6.3 \times 10^{-2}$	1.9	$1.2 \times 10^{-2}$
1.3	$5.0 \times 10^{-2}$	2.0	$1.0 \times 10^{-2}$
1.4	$4.0 \times 10^{-2}$	2.1	$7.9 \times 10^{-3}$
1.5	$3.2 \times 10^{-2}$	2.2	$6.3 \times 10^{-3}$
1.6	$2.5 \times 10^{-2}$	2.3	$5.0 \times 10^{-3}$

\* From Clark and Lubis (1917), page 13.

normal acid  $(H^+) = .01$  or  $10^{-2}$  or pH 2.0. As the hydrogen ions increase in number, the hydroxyl ions must decrease in number, since their product equals  $10^{-14}$  (equation 3). Thus, pH 10.0 or pOH 4.0 represent the same solution. Table 1 gives the values of pH by whole numbers. All the figures in the same horizontal line represent the same solution. Thus, neutrality is shown by  $1 \times 10^{-7}$  hydrogen ions per liter, .0000001 N hydrogen ions, pH 7.0,  $1 \times 10^{-7}$  hydroxyl ions per liter, .0000001 N hydroxyl ions and pOH 7.0.

The fractional values of pH may be obtained as follows:  $1 \times 10^{-8} = \text{pH } 2.0$ ;  $2 \times 10^{-8} = \text{pH } 1.7$ , for the logarithm of 2.0 is .3. This, added to the exponent  $-2.0 = -1.7$  and, the minus sign being understood, equals pH 1.7. Table 2 gives the values in numbers for every tenth pH.

It will be noted that the more acid solutions are represented by the smaller pH values. For pH 1.0 is more acid than pH 1.3. Since these numbers are exponents every even pH represents a tenfold increase in acidity. Thus pH 1.0 is ten times as acid as pH 2.0; and pH 1.0 is a hundred times as acid as pH 3.0.

*Strength of Acids.*—The  $H^+$  (hydrogen ion) is the portion of any acid which gives to it its acid character. The  $(H^+)$  (hydrogen-ion concentration) determines the degree of activity of the acid. The slightly dissociated acids we call weak; those highly dissociated, strong. Acetic and carbonic acids are weak acids. HCl is a very strong acid. In the same concentration, HCl has fifty times as many ions as acetic acid or a thousand times as many ions as carbonic acid, and is proportionally active. Table 3 gives the pH of HCl and acetic acid solutions.

The very strong acids, as HCl, show a characteristic which the weaker acids do not possess—the dissociation increases

TABLE 1 \*

Hydrogen-ion concentration		pH	Hydroxyl-ion concentration	pOH
Acid solutions	$1 \times 10^0$	1.0 N	0.0	$1 \times 10^{-14}$ 0.000000000001 N 14.0
	$1 \times 10^{-1}$	0.1 N	1.0	$1 \times 10^{-13}$ 0.000000000001 N 13.0
	$1 \times 10^{-2}$	0.01 N	2.0	$1 \times 10^{-12}$ 0.000000000001 N 12.0
	$1 \times 10^{-3}$	0.001 N	3.0	$1 \times 10^{-11}$ 0.000000000001 N 11.0
	$1 \times 10^{-4}$	0.0001 N	4.0	$1 \times 10^{-10}$ 0.000000000001 N 10.0
	$1 \times 10^{-5}$	0.00001 N	5.0	$1 \times 10^{-9}$ 0.000000000001 N 9.0
	$1 \times 10^{-6}$	0.000001 N	6.0	$1 \times 10^{-8}$ 0.000000000001 N 8.0
Neutrality	$1 \times 10^{-7}$	0.0000001 N	7.0	$1 \times 10^{-7}$ 0.0000001 N 7.0
	$1 \times 10^{-8}$	0.0000001 N	8.0	$1 \times 10^{-6}$ 0.000001 N 6.0
	$1 \times 10^{-9}$	0.00000001 N	9.0	$1 \times 10^{-5}$ 0.00001 N 5.0
	$1 \times 10^{-10}$	0.000000001 N	10.0	$1 \times 10^{-4}$ 0.0001 N 4.0
	$1 \times 10^{-11}$	0.0000000001 N	11.0	$1 \times 10^{-3}$ 0.001 N 3.0
	$1 \times 10^{-12}$	0.00000000001 N	12.0	$1 \times 10^{-2}$ 0.01 N 2.0
	$1 \times 10^{-13}$	0.000000000001 N	13.0	$1 \times 10^{-1}$ 0.1 N 1.0
Alkaline solutions	$1 \times 10^{-14}$	0.000000000001 N	14.0	$1 \times 10^0$ 1.0 N 0.0

\* From Henderson (1919), page 482.

one gram of hydrogen per liter, tenth normal solutions contain .1 gram of hydrogen, etc.

To write out the actual value of such small fractions as millionth normal or millionth of a gram of ionized hydrogen is cumbersome, and to represent graphically one-tenth of a gram and one thousand millionth of a gram is impossible, unless one uses logarithmic notation. Sörensen suggested this form of expression because in the electrometric method the results are cal-

with the dilution. Tenth normal HCl is about 91 per cent dissociated; hundredth normal, 96 per cent; and thousandth normal almost 100 per cent. The important factor of the pH is the amount of acid present, for if one dilutes normal HCl tenfold, there is very little more than one-tenth the hydrogen-ion concentration.

The strength of acids may be compared by their dissociation or ionization constants. For weak acids one may show by an application of the mass law exactly as has been shown for water (equation 1)

$$\frac{(H^+) \times (A^-)}{(HA)} = K, \quad (7)$$

or

$$(H^+) = K \frac{(HA)}{(A^-)}, \quad (8)$$

where  $(H^+)$  is the hydrogen-ion concentration,

$(A^-)$  is the anion concentration.

$(HA)$  is the concentration of the undissociated acid.

$K$  is the dissociation constant of the acid.

When the concentration of the acid which is undissociated is equal to the dissociated part, or, in other words, when the acid is half dissociated, one may write the equation:

When  $(A^-) = (HA)$  then  $(H^+) = K$ ,

and the  $(H^+)$  is the dissociation constant.

Since it is not possible always to determine the half dissociation point, it is convenient to determine the dissociation constant in another way. The salts of weak acids are almost completely dissociated, yielding a large number of the same anions as those of the acid. By the mass law, the ionization of the acid is repressed, and in amount proportional to the amount of salt present. Thus, assuming the salt to be completely dissociated and applying an equation similar to equation 7, one finds

$$(H^+) = K \frac{(HA)}{(MA)} \quad (9)$$

where  $(HA)$  is the acid and  $(MA)$  is the salt present. When  $(HA) = (MA)$ , then  $(H^+) = K$ . In other words, when the amount of salt is equal to the amount of acid, the  $(H^+)$  is the dissociation constant of the acid.

TABLE 3 \*

pH OF HCl AND ACETIC ACID	pH
1 N HCl .....	1.0
0.1 N .....	1.07
0.01 N .....	2.02
0.001 N .....	3.01
0.0001 N .....	4.00
1 N $\text{CH}_3\text{COOH}$ .....	2.36
0.1 N .....	2.86
0.01 N .....	3.36
0.001 N .....	3.86

TABLE 4 \*

DISSOCIATION CONSTANTS OF SOME ACIDS	pH
Salicylic .....	$1.0 \times 10^{-5}$
Tartaric .....	$1.0 \times 10^{-3}$
Hippuric .....	$2.2 \times 10^{-4}$
Acetacetic .....	$1.5 \times 10^{-4}$
Lactic .....	$1.35 \times 10^{-4}$
Carbon dioxide .....	$3.0 \times 10^{-7}$
Acetic .....	$1.86 \times 10^{-5}$
Boric " .....	$1.7 \times 10^{-9}$

\* From Michaelis (1914), page 11.

\* From Michaelis (1914), page 23.

Thus, when the acid is half dissociated, or when a weak acid is present with an equal amount of its salt, the  $(H^+)$  or pH gives a direct numerical value to  $K$  or the dissociation constant. The greater the value of  $K$ , the stronger the acid. Table 4 gives the dissociation constants of some acids in terms of the numerical value and also of pH.

*Determination of Acidity.*—The strength of acids is subject not only to theoretical consideration, but also to experimental verification. Sörensen (1909-12), Michaelis (1914), Clark and Lubs (1916-17), have given details of the methods. The two principal methods in use are: (1) The electrometric, and (2) the colorimetric.

1. *Electrometric Method.*—The standard method is the hydrogen electrode, or gas chain, or electrometric. This is based upon the principle originated by Nernst, that if one connects two solutions of the same substance, in different concentrations, a current is produced which is proportional to the difference in concentrations. Conversely, if one knows the concentration of one solution and the voltage, one can calculate the concentration of the other. This principle has been applied to determine the hydrogen-ion concentration of any solution. One connects the sample on the one side with platinized platinum saturated with hydrogen and on the other side with a calomel-mercury-KCl cell. From the voltage given, one calculates the hydrogen-ion concentration of the solution. This method requires expensive apparatus and is so difficult that only specially equipped laboratories can use it. It is also so time-consuming that few determinations can be made in a day. Because of its accuracy, however, new problems necessitate its use.

2. *Colorimetric Method.*—Based upon measurements made by the electrometric, Sörensen devised the colorimetric method. Indicators are used to measure the hydrogen-ion concentration. There is a zone of hydrogen-ion concentration in which each indicator develops its characteristic color changes. The method requires a series of standard buffer solutions of which the pH is accurately known. One adds the proper indicator, in the same amount, to equal portions of the standards and the sample. The colors are then compared and the pH of the sample is taken as the pH of the standard to which it is closest in color. This is easy and rapid, and gives values which are accurate for all clinical procedures. The essentials of this method are: (1) A set of standard buffer solutions, and (2) proper indicators.

*Buffers.*—The term "buffer" is the English equivalent of the German "Puffer" which Sörensen adopted from the French "tampon." It means a solution which will hold the reaction constant, or nearly so, when acid or alkali is added to it. Two types of buffer action are clearly understood. If a weak acid is present in solution with its salt, the addition of acid or alkali does not cause a great change in reaction, for the acid is only slightly dissociated and the salt is almost completely dissociated. The ionization of the salt represses the ionization of the acid (equation 9). The pH is dependent upon the proportion of the acid to the salt. Therefore, until all the acid has been converted into the salt, the addition of a

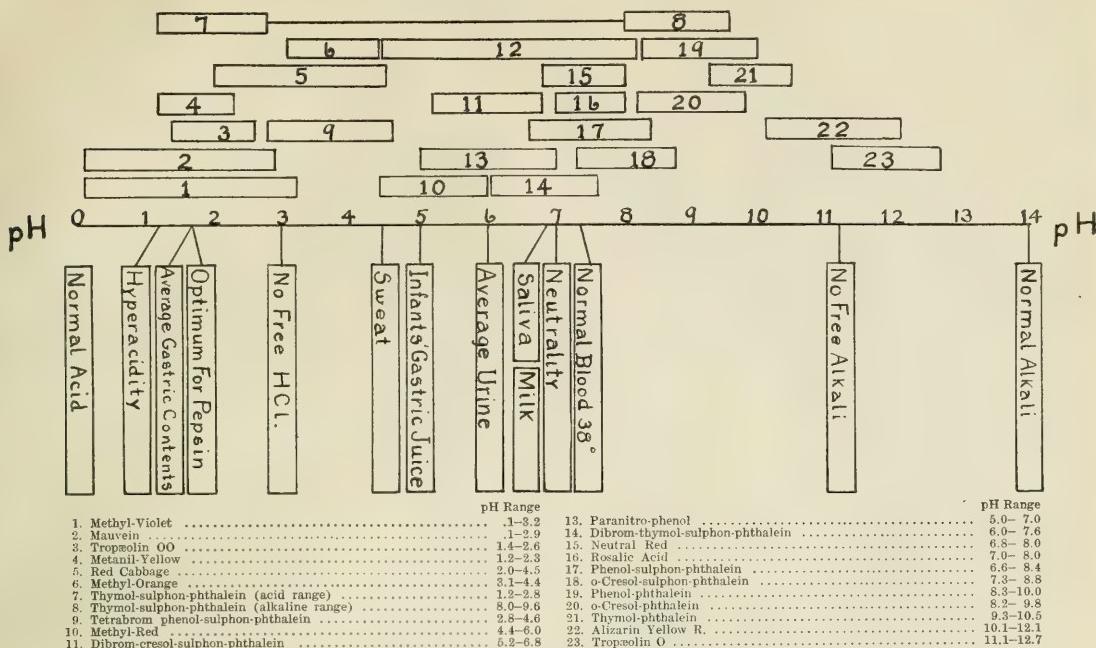


FIG. 1.—End Points of Common Indicators.

strong alkali will not make the solution very alkaline, or until all the salt has been converted to the acid, the addition of a strong acid will not make the solution very acid. For example, if there is a mixture containing equal parts of tenth normal acetic acid and sodium acetate, the reaction will be pH 4.75. Not until all the acid is neutralized by the addition of an alkali will the solution be pH 7.0, or neutral; and not until all the sodium acetate has been changed into acetic acid by the addition of an acid will the reaction equal pH 3.0, or "no free HCl."

A second type of buffer action is similar to the first, but still more stable. If, upon addition of an acid or an alkali to a solution, a compound is formed which in itself is very slightly dissociated, there will be a very small change in the hydrogen-ion concentration. When a liter of fifteenth normal acid sodium phosphate, in itself a very weak acid, which gives a pH of 4.5, is neutralized with a liter of fifteenth normal alkali, it gives alkaline phosphate with a pH of 9.0. An equal change is brought about in a liter of water by 1 c. c. of the same alkali. Protein has this property of forming compounds with either acids or bases and yielding slightly dissociated compounds. In general, dibasic or polybasic acids, with one or more  $H^+$  neutralized, are in this category.

Other substances act as buffers through their ability to absorb or adsorb acids and alkalis. Charcoal and colloids probably fall into this class. Their action is at present not

well understood. The question has often arisen as to which buffer is the best. Koppel and Spiro (1914) have shown that all buffers are equally good, but that each is strongest in a certain zone. They demonstrated that the maximum buffer value occurs at the ionization constant, or when the acid and salt are present in equal amounts. Practically, one selects that buffer solution in which the ionization constant is nearest the desired pH.

*Indicators.*—So many indicators are available that one must use considerable judgment in selecting those most suited to gastric analysis. Controversies were carried on in the last fifty years over the advantages of certain indicators for biological fluids, such as blood and stomach contents. The difficulties have disappeared in the light of our fuller knowledge. A great many substances show changes in color in acid and alkaline solutions. If strong acids and strong bases are titrated, almost any of the common indicators can be used. That is because their "end point" or color change is within the change of pH produced by a single drop of strong acid or alkali. When protein or other buffers are present, the indicators give very different results. Fig. 1, shows the end point, or as it will be seen, end "zones" of some of the common indicators.

Indicators which give accurate values in pure solutions may be at fault in biological fluids. Indicators give false values in these fluids because of the presence in them of protein or

salt. These errors have been studied by Sörensen and, when serious, led him to reject the indicator.

To determine the pH of gastric contents, one must first define the necessary range of pH. At pH 3.0, 100 c. c. of contents equals only 1 c. c. of tenth normal free HCl. Large amounts of organic acids or acid protein may be present without increasing the pH. Hence, pH 3.0 should be taken as the least acid point for the study of free HCl. If 70 c. c. of tenth normal free HCl are present in 100 c. c., which is the maximum acidity of stomach contents, the reaction is pH 1.2. Several indicators that cover this range have been recommended for determining the pH of biological fluids. They are shown in Table 5.

TABLE 5  
INDICATORS FOR ACID SOLUTIONS

	pH
1. Methyl-violet 6B extra.....	0.1-3.2
2. Mauvein (Grübler) .....	0.1-2.9
3. p-Benzol-sulphonic-acid azo-diphenylamin. Tropæolin OO.14-2.6	
4. m-Benzol-sulphonic-acid azo-diphenylamin. Metanil yellow .....	1.2-2.3
5. Red cabbage .....	2.0-4.5
6. p-Benzol-sulphonic-acid-azo-dimethylamin. Methyl-orange .....	3.1-4.4
7. Thymol-sulphon-phthalein .....	1.2-2.8

Of this list, methyl-violet and mauvein fade rapidly, tropæolin OO in a few days. The more acid the solutions, the more rapidly they fade. Sörensen says that methyl-violet and mauvein are unreliable in the presence of salts and all the azo dyes in the presence of proteins. He does not include tropæolin OO in the list of indicators which are unreliable in the presence of protein. Christiansen found, however, that for stomach contents it is entirely unreliable. Michaelis found that methyl-orange is also unsatisfactory for stomach contents. Walbum studied red cabbage and says that it is reliable even in the presence of genuine protein, but it does not cover the range of stomach contents. Thymol-sulphon-phthalein, studied by Clark and Lubs (1917), is the only indicator which meets the requirements for determining the pH of gastric contents.

The range of neutrality is well covered by the following indicators, shown in Table 6:

TABLE 6  
INDICATORS FOR NEUTRAL SOLUTIONS

	pH
1. Litmus .....	4.4-8.0
2. Neutral red .....	7.0-8.0
3. Rosalic acid .....	6.8-8.0
4. Phenol-sulphon-phthalein .....	6.6-8.4
5. Paranitro-phenol .....	5.0-7.0
6. Dibrom-thymol-sulphon-phthalein .....	6.0-7.6

The third zone of interest is when thousandth normal alkali is present so that it, like HCl, may be considered free. When 100 c. c. of solution equal 1 c. c. of tenth normal alkali,

.001 N NH<sub>3</sub> is pH 10.27 and .001 N NaOH is pH 11.13. This range is covered by the following indicators shown in Table 7:

TABLE 7  
INDICATORS FOR ALKALINE SOLUTIONS

	pH
1. Phenol-phthalein .....	8.3-10
2. o-cresol-sulphon-phthalein .....	7.2- 8.8
3. Thymol-sulphon-phthalein .....	8.0- 9.6
4. o-cresol-phthalein .....	8.2- 9.8
5. Thymol-phthalein .....	9.3-10.5
6. p-Nitrobenzol-azo-salicylic-acid. Alizarin yellow R.....	10.1-12.1
7. p-Benzol-sulphonic-acid azo-resorcin. Tropæolin O.....	11.1-12.7

Sörensen says that alizarin yellow R and tropæolin O are not very reliable, but that phenol-phthalein and thymol-sulphon-phthalein are excellent in the presence of protein. Clark and Lubs find o-cresol-sulphon-phthalein, thymol-sulphon-phthalein and o-cresol-phthalein reliable. There has been no special biological interest in so alkaline a range, but in determining the total buffer value of stomach contents titration to the point of free alkali becomes important. The figure shows a sufficient number of tested indicators to meet all the requirements for the determination of the acidity of gastric contents by the colorimetric method.

*The Acidity of Stomach Contents.*—From a consideration of the pH of solutions and the strength of acids, the nature of acidity of stomach contents becomes clear. For if we add HCl to stomach contents, the hydrogen-ion concentration will not reach pH 3.0 until all the protein has been converted into acid protein and all the organic acids have been freed from their combination with protein by HCl. For this reason, the sum of all acid factors is called total acidity, of which the acidity from neutrality to pH 3.0 is combined acidity and from pH 3.0 to pH 1.2, free HCl.

*Free HCl.*—At pH 3.0, 100 c. c. of stomach contents represent 1 c. c. of tenth normal HCl not combined with protein. This is true regardless of the presence of large amounts of free organic acids. For if there are 100 c. c. of tenth normal lactic acid present and half is free, the acidity is  $1.35 \times 10^{-4}$ , or pH 3.85, and for 100 c. c. of tenth normal acetic acid of which half is free,  $1.86 \times 10^{-5}$ , or pH 4.75. Even in these exaggerated examples the sample would not be as acid as "no free HCl." To give accurate titration values for free HCl, an indicator must be without protein and salt errors, and have a very sharp end point at pH 3.0. According to Christiansen, none meets these conditions. Determination of the pH of gastric contents by a colorimetric method, with thymol-sulphon-phthalein, is proposed in Paper II.

*Total Acidity.*—The total acidity of stomach contents is the amount of free acid plus the acid combined with protein and other buffers. It is usually determined by titration with phenol-phthalein. The end point with this indicator is approximately pH 8.4-10.0 and not neutrality. For this reason, Christiansen favored the use of litmus, which changes at approximately pH 7.0, or neutrality. Only if the protein and other substances, as eaten, are neutral, does the titration to pH 7.0 represent the amount of acid produced by the stomach. In our opinion, neither of these end points, pH 7.0 nor 8.4, is

correct. It is more rational to titrate to pH 7.4. Titration value then represents the acid of the stomach contents which must be neutralized before they reach the reaction of the blood. Palmer and Henderson chose this as the end point for the titration of urine. It does not, however, and for the same reason as above, represent the amount of acid produced by the stomach. For example, let us assume that the ingested bread had a reaction of pH 3.0; then the free HCl represents the amount of acid produced by the body. The titration is too great by the amount of the combined acid. If the bread has a reaction of pH 8.0, the values obtained are less than the HCl secreted. If information of this character is desired, methods other than titration must be resorted to, for there is really no correct predetermined end point at which the total acid can be measured. This has led us to believe that measurement of the buffer value of stomach contents yields more accurate information than titration of the total acid to pH 7.0 or 8.4. A method for determining the buffer value of stomach contents by titration, using thymol-sulphon-phthalein as an indicator, is proposed in Paper III.

*Significance of pH Values in Gastric Contents.*—The importance of considering the acidity of stomach contents in terms of hydrogen-ion concentration becomes evident when one analyzes the recent literature on peptic digestion. Sörensen, in his work on enzymes, showed that acidity of the medium was as important a factor as temperature in enzyme action. Only within certain narrow limits of reaction is pepsin active. The optimum reaction is approximately pH 1.65 for the action of pepsin on acid egg albumen. This is in close agreement with the figures of Michaelis and Davidsohn who record the optimum for peptic action on casein as pH 1.8. Michaelis and Mendelsohn (1914) and Northrup (1919) record the optimum on edestin as well as casein at the same acidity. They show that this is due to the hydrogen-ion concentration and not to any specific qualities of HCl, since they were able to duplicate these values with another mineral acid,  $\text{HNO}_3$ , and two very strong organic acids, tartaric and oxalic. Christiansen (1912) finds the optimum for human pepsin to be pH 1.55. If the amount of acid is greater or less than this amount, the amount of protein digestion becomes smaller. Concentrations of acid greater than pH 1.3 permanently injure and finally destroy the enzyme. If the reaction is not more acid than pH 3.0, peptic action is very poor, and at pH 4.0 is almost lacking. The fact that pepsin requires a solution of definite pH for its action is supplemented by our knowledge of the reaction of the gastric juice. Foà (1905) and Tangl, working with pure gastric juice, determined the pH by the electrometric method and found it to be pH 1.3. Fränkel, Michaelis and Davidsohn, and Christiansen, found that the normal of the contents after an Ewald meal lay between pH 1.6 and 1.5. Thus the normal hydrogen-ion concentration of the gastric juice makes an ideal medium for the optimum action of pepsin.

#### SUMMARY

- To determine the acidity of gastric contents by methods based upon sound principles, one must consider acidity in terms of ionization and hydrogen-ion concentration.

- The expression of gastric acidity in terms of pH (hydrogen-ion concentration) brings out clearly the relation between acidity and peptic digestion.

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## DETERMINATION OF THE ACIDITY OF GASTRIC CONTENTS

### II. THE COLORIMETRIC DETERMINATION OF FREE HYDROCHLORIC ACID

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To determine the free hydrochloric acid in gastric contents a test meal is given and the contents withdrawn after a definite time. The test meal most frequently used is the one introduced by Ewald, and consists of a cup of clear weak tea or a glass of water and a piece of bread, which is withdrawn after one hour. The hydrochloric acid is then determined. According to the principles underlying them we may class the methods in three groups: (1) Titration methods; (2) methods involving chemical reactions; (3) methods for measuring the hydrogen-ion concentration.

**1. Titration.**—Ten cubic centimeters of contents, filtered or unfiltered, are titrated with an alkali and a suitable indicator. The indicators most frequently used are Töpfer's (dimethylamido-azo-benzol), methyl-orange, tropaeolin OO, alizarin sulphonate, and congo paper. An alkali of known strength, usually tenth normal, is added to the contents containing the indicator until the latter changes color, or, as it is called, reaches its "end point." The color change takes place at a certain definite concentration of acid. These particular indicators have been selected because they change color at the point at which free HCl is approximately neutralized. From the number of cubic centimeters of alkali used one calculates the number of cubic centimeters of tenth normal acid in 100 c. c. of stomach contents. For example, if 5 c. c. of tenth normal alkali neutralize the acid in 10 c. c. of the sample, 50 c. c. of tenth normal alkali neutralize the acid in 100 c. c.; that is, 100 c. c. of stomach contents contain 50 c. c. of tenth normal HCl.

Care must be taken to select the indicator which has the correct end point. In pure solutions of HCl almost all indicators give approximately the same result. A single drop of alkali produces the change from acidity to alkalinity. When other substances—phosphates, carbonates, proteins or salts of organic acids—are present with the HCl, as in stomach contents, different indicators give widely different results, because these substances act as buffers. In the zone between thousandth normal acid and thousandth normal alkali, the change produced by a single drop of alkali is very small when buffers are present. The indicators change at different places in this middle zone. For this reason we are accustomed to divide the titration into two parts, the part up to thousandth normal acid, and the part from thousandth normal acid to

alkalinity. The first represents the *free HCl* and the other the *combined acid*, the sum of the two equaling the *total acidity*.

**2. Chemical Reactions.**—The following two methods will serve as examples of the methods involving chemical reactions.

**Günzburg's Reagent:** This reagent is a mixture of phloroglucin and vanillin. Though not an indicator, since it does not change color with varying concentrations of acid, it can be used to determine the free HCl in stomach contents. When a drop of this reagent is heated with a drop of contents in a porcelain dish a chemical change takes place. If no HCl is present, a yellow color develops; if HCl is present, a red color develops. Christiansen (1912) gives an excellent account of the chemistry of and procedure with this method. Ordinarily one merely uses this method to demonstrate the presence or absence of free HCl. One can use it in titrating by repeating the procedure after each addition of alkali until the test is no longer positive.

**Sahl's Reagent:** This is a mixture of potassium iodide and potassium iodate, which liberates iodine in the presence of acid. The liberated iodine is titrated with thiosulphate and starch.

**3. Measurement of Hydrogen-Ion Concentration.**—The true acidity of solutions is the amount of ionized hydrogen per unit volume. For determining the hydrogen-ion concentration there are two principal methods. The more accurate is the electrometric. Developed by Sörensen (1909), it has become the standard by which all other methods for measuring acidity must be judged. The colorimetric method is less accurate but simpler. This was also developed by Sörensen, who studied the hydrogen-ion concentration of test or standard solutions made from pure chemicals. In these standard solutions, suitable indicators give a definite color value or "nuance", so that one can determine the true acidity of a sample by matching it with the color standards containing the same dye in the same amount.

Many indicators which are useful in general chemistry are unfit for the colorimetric determination of gastric contents, but a sufficient number of tested indicators are available. Hawk's "Physiological Chemistry" (Chap. VIII) contains an excellent account of the principles of the colorimetric method thus applied. There are two clinical methods based

upon the colorimetric—that of Müller (1909) and that of Michaelis and Davidsohn (1910).

*Müller's method* involves the use of standard solutions containing known amounts of HCl and also the indicator tropaeolin OO. The stomach contents and standards are put into tubes of the same diameter and the same amount of indicator is added to each. One compares the color of the contents with the standard which most nearly matches it, and the amount of HCl is estimated. Since these indicator solutions fade, Müller has devised a color chart to replace the standards.

*Michaelis and Davidsohn's method* is called by the authors a rough or orientation procedure. By the use of seven properly selected indicators the range of hydrogen-ion concentration of any stomach content from alkalinity to hyperacidity can be approximately determined.

#### DISCUSSION

These three types of method have been critically analyzed by Michaelis and Davidsohn (1910) and by Christiansen (1912). Both used the electrometric method as a check. They agree that titration methods with indicators give false results. Some of the faults of the methods are due to the fact that the indicators are not suited to the purpose for which they were used. In some the end point is not correct, as with Töpfer's indicator; in others it is not sharp, as with methyl-orange or tropaeolin OO. Again, the indicator may be unsuited to solutions containing protein or salt, as congo-red or methyl-violet. Fundamentally, however, the titration method itself is faulty, for titration of an acid gives only the total amount of the acid; it cannot give the effective amount or, in other words, the hydrogen-ion concentration. Physiologically this is the important factor. In tenth normal acetic acid there are no more hydrogen-ions than in thousandth normal HCl, for the acetic acid is only slightly dissociated. Yet tenth normal acetic acid neutralizes a hundred times as much alkali as thousandth normal HCl. The hydrogen-ion concentration of the acid determines its action in the gastric contents.

Of the chemical reagents, Günzburg's gives values that are accurate. Phloroglucin and vanillin do not react to lactic, butyric or acetic acids, so that even if these are present in the gastric contents, they will not affect the results. But the method is so tedious that it is not practical for clinical purposes. Sahl's reagent has all the disadvantages of the indicators used in the titration methods. Hawk recommends it for its sharp end point, but holds that its values are not accurate because it measures acidities other than free HCl. It does not show the effective, but only the total "free" acid.

Of the methods for measuring the hydrogen-ion concentration, the *electrometric* is so difficult that only specially equipped laboratories can use it, whereas the *colorimetric* is correct and easy to apply. However, no accurate method is at present based upon the colorimetric principle, inasmuch as all the indicators which have been used yield large errors. Müller's method was an effort to apply this procedure to obtain accurate quantitative data. That he failed has been

shown by Michaelis and Davidsohn, who asserted that the method was not devised with a clear understanding of the underlying principles. This is true, but checks and corrections could have been supplied. The fact that the colors fade rapidly, as Müller himself pointed out, is a more valid objection. Christiansen (1911) showed that in the presence of protein, as in stomach contents, tropaeolin OO gives results that are not accurate; hence Müller's method must be rejected.

Michaelis and Davidsohn pointed out that the indicators available were not exact, and that their method is useful merely for orientation. It requires seven indicators and seven samples. The hydrogen-ion concentration is physiologically significant in the range of only two of these indicators, methyl-violet and tropaeolin OO. The information obtained is not exact enough to be of help in instituting therapeutic procedures. Nevertheless, since the colorimetric method is correct in theory, we have used it as a basis for the method which we shall now present.

#### COLORIMETRIC DETERMINATION OF FREE HCl

The clinical method for the determination of free HCl in gastric contents is based upon the colorimetric method for

TABLE I

pH	(H <sup>+</sup> )	N	C. c. of .1 N HCl in 100 c.c. of contents	HCl, .1 N c. c.	KCl, .1 N c. c.	Water up to 100 c.c.
1.3	.050	.054	54	51.0	49	
1.4	.040	.044	44	41.5	50	
1.5	.032	.035	35	33.0	50	
1.6	.025	.027	27	26.3	50	
1.7	.020	.022	22	20.5	50	
1.8	.016	.017	17	16.6	50	
1.9	.012	.013	13	13.1	50	
2.0	.010	.010	10	10.6	50	
2.2	.006	.006	6	6.7	50	
2.4	.004	.004	4	4.2	50	
2.6	.0025	.0025	2.5	2.9	50	
3.0	.001	.001	1	CH <sub>3</sub> COOH .1 N 98 c.c.	NaOH .1 N 2 c.c.	

The first column shows pH, and the second (H<sup>+</sup>). Both represent the hydrogen-ion concentration. The third column, N, represents the normality of the HCl. The fourth column represents the number of cubic centimeters of .1 N HCl in 100 c. c. of stomach contents. The last columns give the composition of the standard solutions.

measuring hydrogen-ion concentration. We shall describe: (A) Expression of acidity; (B) standards; (C) indicators; (D) color comparator; (E) materials; (F) procedure; (G) checks and results.

A. *Expression of Acidity*.—The true acidity or hydrogen-ion concentration is calculated from the gram molecular or normal solution of HCl. A liter of normal HCl contains 1 gram of ionized hydrogen (assuming dissociation to be complete). A tenth normal solution contains .1 gram, or, written in other equivalent forms, is 10<sup>-3</sup> or 1 × 10<sup>-3</sup> or pH 1.0.

The last notation was devised by Sörensen and represents the negative exponent expressed as a number with the minus sign omitted. Thus hundredth normal HCl can be expressed as .01 N or in terms of hydrogen-ion concentration, .01 or  $10^{-2}$  or pH 2.0.

**B. Standard Solutions.**—Standard solutions are made according to the method of Clark and Lubs (1916, 1917) from pH 1.3 to 3.0. With the exception of the least acid (pH 3.0), which is tenth normal acetic acid, they are mixtures of HCl and KCl. The amounts of HCl and KCl are given in Table 1. The color which they give with the indicator is shown in Fig. 1. If the standards are not available this figure can be used in their place. As many standards can be made as desired. To avoid making the set too bulky we have used as few as possible—pH 1.4; 1.6; 1.8; 2.0; 2.4; 3.0—six in all. For the most accurate work we recommend a series of standards made up for every .1 pH. These color differences are easily distinguishable and a closer approximation can be obtained. The excellent glycocoll and citrate standards of Sörensen cover the range of gastric acidity. The HCl and KCl standards were chosen instead because it was easier to purify the substances and to make up the solutions. For very rough work, where it is desired to know simply whether there is any or much HCl, one can make the standards by diluting tenth normal HCl. In fact, after one becomes accustomed to the method and the eye is trained to the color values, rough approximation can be made without any standards.

**C. Indicator.**—The range of acidity of stomach contents for free HCl is pH 1.2 to pH 3.0—high acidity to no free HCl. From the indicators which cover this range, we chose thymol-sulphon-phthalein (Clark and Lubs). This indicator exactly covers the range, is brilliant, permanent and free from errors due to proteins and salts. Clark and Lubs mention its applicability to stomach contents. The color of the indicator is wine red at pH 1.2, orange at pH 2.0 and yellow at pH 3.0. These are shown in Fig. 1. The color will fade gradually at high temperatures and in bright sunlight. It lasts for months if the colored standards (when not in use) are kept in a closed box at room temperature. We use a .2 per cent alcoholic solution. We make the indicator concentrated so that one drop is sufficient for each cubic centimeter of standard or sample. The drop used, which, for alcoholic solutions, an ordinary medicine dropper or pipette will deliver, is equivalent to .02 c. c. After the standards have been made, this amount of the indicator solution is added for each cubic centimeter, and the same amount for each cubic centimeter of the sample. This gives the minimum dilution of the standards and sample and is the same for both.

Inasmuch as the color of thymol-sulphon-phthalein changes most markedly at points corresponding to normal or slightly diminished gastric acidity, it is most useful in the most important range. Strongly acid solutions can be brought to this range by simple dilutions. Doubling the water halves the concentration of acid. Titration by such dilution has been suggested by Hawk. Moreover, dilution has another value. If

the stomach contents are colored, they tend to obscure the color resulting from the indicator, and by adding water we dilute this extraneous color. The color of the sample will then more closely approximate one of the standards. Hence the dilution makes the color comparison more accurate for two reasons: (1) It diminishes the color interference, and (2) it brings the reaction to the acidity at which the indicator gives the sharpest readings.

**D. Color Comparator.**—It is convenient to use a small color comparator such as has been described by Walpole (1911). The principle is to examine the tubes by transmitted light. The tubes are placed in a frame which cuts off the light around them and exposes them only through a small circular opening. There should be three compartments side by side, so that the sample may be placed between the two standards nearest in color. By rearranging the order of the tubes the difference in color appears more marked. Each compartment should be deep enough to hold two tubes. This facilitates the reading of colored or turbid solutions. A tube of contents without any indicator is placed behind the standard in each of the two end compartments, and in the middle compartment a tube of clear water is placed behind the contents containing the indicator. In this way very dark or turbid contents can be sharply read. A diagram, Fig. 2, shows the arrangement of the tubes.

The colorimeter is shown closed, in Fig. 3; opened, in Fig. 4; opened and the tubes properly arranged, in Fig. 5; and in position for reading, in Fig. 6. The purpose of the lid is to cut off all light except that which comes through the ground glass. The partitions are to prevent light from being reflected from the adjacent tubes. The movable sleeve protects the tubes from light when not in use. We wish to express our thanks to Dr. H. H. Young and Dr. D. M. Davis for helpful suggestions in planning the mechanical details of the colorimeter, and to Mr. H. I. Hughes for the construction of the model in the Brady Urological Institute experimental instrument shop.

If no color comparator is available, the tubes can be placed in a small test tube-rack on the window-sill. At a distance of from 6 to 10 feet, the colors appear sharper. The comparator is, however, more satisfactory.

**E. Material.**—Our material consisted of gastric contents removed one hour after an Ewald test meal of 250 c. c. of water and 25 grams of bread. A few cases of contents from fasting stomachs are included in our series. The contents were either filtered or unfiltered. In the latter case we centrifuged at high speed for 10 minutes and drew off the supernatant fluid. In this way we obtained considerably more material and thus had a supply for duplicates and checks on the method. A good many of the contents were turbid or colored and some contained a small amount of bloody mucus, but all samples were accepted for analysis.

**F. Procedure.**—Take 2 c. c. of filtered or centrifuged contents recovered from an Ewald test meal in a test-tube 11 mm. in diameter. Add two drops or .04 c. c. of .2 per cent thymol-sulphon-phthalein in 95 per cent alcohol. Place in a color



FIG. 1.—Shows the color nuance of standard solutions containing .02 c. c. of 2% thymol-sulphon-phthalein in alcohol, per c. c. of solution, and also the corresponding value in terms of pH and in c. c. of tenth normal HCl per 100 c. c. of gastric contents.

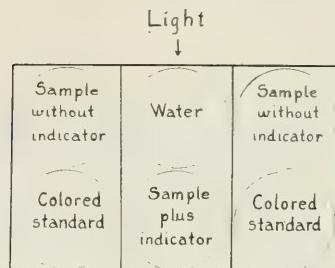


FIG. 2.—Diagram, showing the arrangement of solutions in colorimeter for making a colorimetric determination.

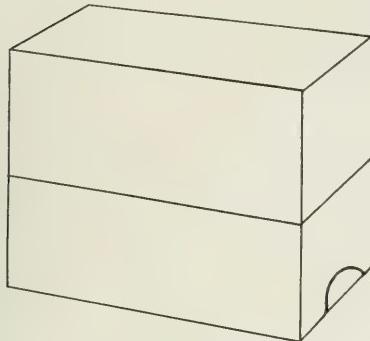


FIG. 3.—Colorimeter closed.

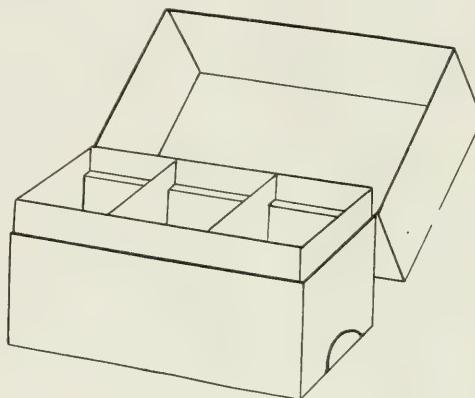


FIG. 4.—Colorimeter ready to receive tubes.

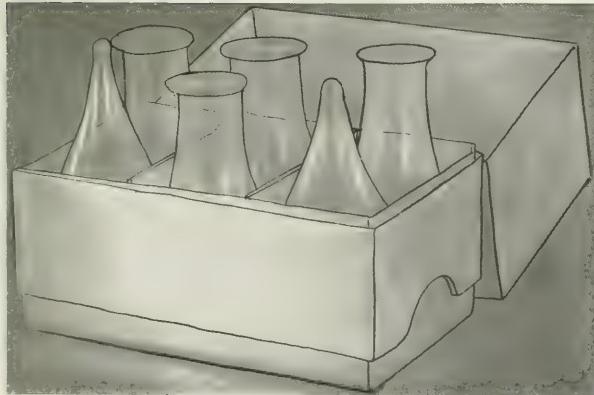


FIG. 5.—Colorimeter and tubes in position.

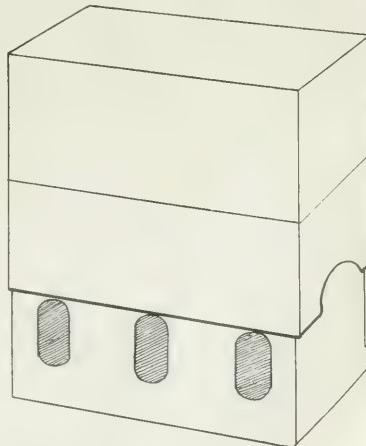
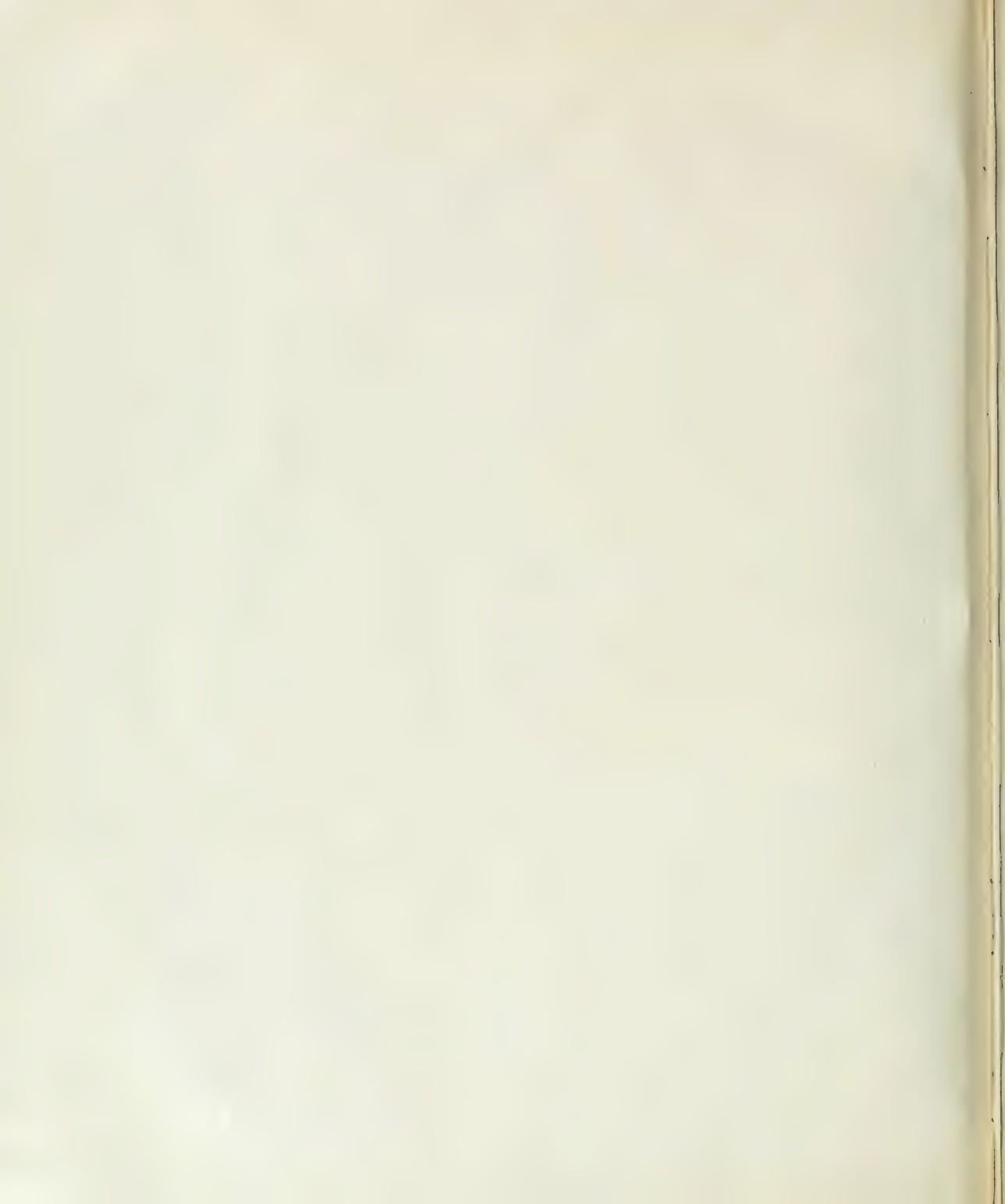


FIG. 6.—Colorimeter in position for reading.



comparator with the standards nearest to it in color. From the figures given in Table 1 estimate the amount of acid present. The results can be read directly in terms of pH, normality, or in cubic centimeters of tenth normal free HCl per 100 c. c. of stomach contents. When the sample is more acid than pH 1.6, dilute the contents with 2 c. c. of distilled water, and add two more drops of the indicator. Multiply the reading by 2, to obtain the acidity of the original sample. Thus, pH 1.3 (54 c. c. tenth normal HCl) on dilution gives pH 1.6 (27 c. c.).

It is not necessary to use the amounts given here. The only requisites are: (1) The indicator must be in the same proportion in the standards and in the sample; (2) the tubes containing the standards and sample must be of exactly the same diameter; (3) no water must be added unless the amount is known and the necessary calculation made. This method is also applicable to stomach contents removed by the fractional method, to other test meal contents, to pure gastric juice, and to other solutions ranging from pH 1.3 to pH 3.0.<sup>1</sup>

*G. Checks and Results.*—The values obtained by direct reading have been checked in four ways. The results are given in Table 2. The checks are: (1) by titration with .1 N alkali, using Töpfer's indicator; (2) by titration with .1 N alkali using thymol-sulphon-phthalein as an indicator; (3) by dilution, as explained above; (4) by the electrometric method.

No determination made was omitted from Table 2. It will be seen that the values agree very closely with those obtained by the electrometric method—within .1 pH. Assuming the values by the electrometric method to be correct and expressing the results in terms of .1 N HCl per 100 c. c. of contents the average difference by our method is .3 c. c.

In this series of determinations by the colorimetric method there is only one case in which there is a significant error (No. 34). This value is too high, judged by titration with either thymol-sulphon-phthalein or Töpfer's. The explanation we offer for this is that the patient had been taking iron and salicylates, which give a color reaction with the indicator. Hence, on dilution the error becomes greater. Direct reading equals 52 c. c.; dilution with an equal volume of water equals 54 c. c.; dilution with three volumes equals 64 c. c. We have found no other drug or combination of drugs which interferes with the determination. Good values are obtained by this method in contents showing high acidities (over 50 c. c.) of free HCl, as can be seen in Nos. 5, 12, 18, 29, 32, 33 and 50. This shows that this indicator is accurate in a range in which no other indicator has proved useful. It also gives as good or better values in the lower ranges. In contents where it is questionable whether free HCl is present or absent No. 45 is of interest. Töpfer's indicator showed free HCl to be present, but by the colorimetric method and electrometric method none was present. The average value of the HCl by our method is 20.0 c. c.; by titration with thymol-sulphon-

phthalein, 19.4 c. c.; by titration with Töpfer's indicator, 24.2 c. c. Since it has been seen that the colorimetric method gives values which are lower than titration with Töpfer's indicator and which agree with those of titration to pH 3.0, and also those of the electrometric method, which is "the court of last appeal," it may be inferred that this method is more

TABLE 2  
CUBIC CENTIMETERS OF .1 N HCl IN 100 C. C. STOMACH CONTENTS

Number of case	Colorimetric	Titration with thymol-sulphon-phthalein	Titration with Töpfer's indicator	pH colorimetric	pH electrometric
1. G23353	9	12	15	2.1	2.0
2. 23319	2.5	2.5	3.8	2.6	2.7
3. 23324	6	6.5	17.5	2.2	...
4. H. R.	—	7	—3	—	...
5. K. C.	64	64	63	1.3+	...
6. F54756	32	31	33	1.5	...
7. 23393	20	20	22	1.7	...
8. M. C.	—	-1	3	—	...
9. H. M.	4	4	7	2.4	...
10. H. N.	1.5	1.5	5.5	2.8	...
11. 23576	—	—1	5	—	...
12. 23607	48	52	—	1.4+	...
13. C. E.	18	19	32	1.7	...
14. 23581	—	-45	-25	—	...
15. 23553	10	12	30	2.0	...
16. 23624	16	16	20	1.8	...
17. 23751	27	28	30	1.6—	...
18. 58919	50	50	50.0	1.3	...
19. T. H.	15	14	16.5	1.8	...
20. F58991	20	21	30	1.6	...
21. 23861	1	1	3	3.0	...
22. 23871	3	3	5	2.6	...
23. 23880	5	6	11	2.3	...
24. 74040	24	23	34	1.6—	...
25. 29991	18	17	26.5	1.8+	...
26. S24089	16	17	29	1.8	...
27. G24094	13	14	26	1.9	...
28. 24276	24	26	32	1.6	...
29. 24091	53	50	55	1.3	...
30. 21452	1	1	6	3.0	...
31. F41452	15	14	21	1.8—	...
32. 9729	50	45	50	1.4+	...
33. G24279	50	51	62	1.3	...
34. 88487	52*	34	39	1.3	...
35. 12442	40	40	46	1.4	...
36. F95016	—	-10	0	—	...
37. G 7582	2	2.5	8	2.6	...
38. G24429	—	-16	0	—	...
39. G24376	4	4	7.5	2.4	...
40. G17077	15	5	12	2.3	...
41. G 2379	10	11	14	2.0	...
42. C. F.	6	5.5	10	2.2	2.1
43. 26480	5	6	9	2.3	2.3
44. 37078	12	10	20	1.9	1.9
45. 27033	—	-1	10	—	3.4
46. 27354	5	5	11	2.3	2.3
47. 27418	12	10	14	1.9	1.8
48. 5986	10	12.5	14	2.0	1.95
49. 27465	—	2.5	5	2.6	2.6
50. V. F.	70	63	70	1.3+	1.2

accurate than those in common use. In addition it is simple and rapid enough for clinical and bedside application.

Much stress has been laid upon the pH or hydrogen-ion concentration of gastric contents because of its importance to the clinician in interpreting stomach findings. In the previous paper, we have shown the correlation between the pH of the contents and the effect on gastric digestion. The limits of peptic digestion are pH 1.3 and 4.0 and the optimum is at pH 1.65. It seems obvious that one should correlate these important facts with medical practice. With the information

<sup>1</sup> All the materials necessary for carrying out the test can be obtained from Hynson, Wescott & Dunning, Baltimore. Complete sets and color comparators, as well as separate standards, tubes and indicator solution are available.

at hand we can say exactly what the optimum of the gastric contents should be and we can estimate how much acid is necessary to produce the optimum reaction in the sample which has been removed. Thus we have at the same time, in the measurement of the hydrogen-ion concentration, a method for diagnosis, an evaluation of the degree of progress and the indications for therapeutic procedures.

#### SUMMARY

1. A new colorimetric method is presented, which determines the amount of free HCl in the gastric contents. A simple color comparison shows both the amount and concentration of the acid.

2. The procedure is: Take 2 c.c. of filtered or unfiltered gastric contents. Add 2 drops of .2 per cent thymol-sulphon-phthalein. Compare the color of the sample with standard solutions containing the same amount of the same indicator.

3. The result can be read directly in terms of pH, normality, or cubic centimeters of free tenth normal HCl in 100 c.c. of gastric contents.

4. The method is accurate and applicable to clinical tests.

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## DETERMINATION OF THE ACIDITY OF GASTRIC CONTENTS

### III. COMBINED ACIDITY AND BUFFER VALUE

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The acidity of stomach contents removed after a test meal is usually measured in several fractions. The total acidity or sum of all the acid factors is composed of free HCl and the combined acid. The combined acid is that portion which remains after the free HCl has been neutralized, and consists of (1) the combined HCl; (2) organic acids; and (3) acid salts. Experience has shown that the combined HCl is practically the same as the combined acid, for organic acids and acid salts play a very small part in gastric acidity. In cases in which no free HCl occurs, the combined acid and the total acidity are identical. Such contents are said to show an "acid deficit" represented by the amount of HCl which must be added to the sample until free HCl is just present. This value indicates the amount of acid which the stomach should secrete, or which, if it fails to secrete, must be added before gastric digestion can progress. The sum of the total acidity and the acid deficit in such cases measures the power of the contents to combine with acid. This value is comparable to the combined acid in cases showing free HCl.

There are three types of methods for the determination of combined acid. According to the principles underlying them, these are: (1) Titration methods; (2) methods involving chemical reactions; and (3) hydrogen-ion concentration measurements.

1. *Titration Methods.*—The usual procedure is to titrate 100 c.c. of contents with an alkali and a suitable indicator.

The indicators most frequently used are phenol-phthalein, litmus, rosalic acid, neutral red and alizarin. These indicators have been selected because their end point is approximately that of neutrality. From the number of cubic centimeters of an alkali of known strength which are required to reach the end point of the indicator, one calculates the number of cubic centimeters of tenth normal acid in 100 c.c. of stomach contents. Titration gives the total acidity from which one must subtract the value of the free HCl. Thus, if 10 c.c. of stomach contents require 7.5 c.c. of .1 N alkali to reach the end point of phenol-phthalein, 75 c.c. of .1 N acid represent the total acid in 100 c.c. of stomach contents. If the free HCl was found to be 50 c.c., then 75 c.c. minus 50 c.c. equals 25 c.c., the value of the combined acid. In practice, one usually adds two indicators to the same sample, as Töpfer's indicator and phenol-phthalein. The colors do not interfere, so that one can titrate the free HCl, and from that point determine the combined acid directly.

If no free HCl is present, one determines the total acidity by titrating with an alkali and phenol-phthalein, as above. One also titrates with an acid and Töpfer's indicator to obtain the acid deficit. These two values are added. Thus, if the total acid equal 12 c.c. of .1 N acid and the acid deficit equals 15 c.c. of .1 N acid, the sum of the two equals 27 c.c. of .1 N HCl per 100 c.c. of stomach contents. This represents the combining power of the contents.

A series of titration methods using several indicators, so as to determine separately combined HCl and organic acids, was devised at the time when it was thought organic acids were present in the stomach contents in considerable amounts and were an important factor in gastric acidity. These methods are no longer used.

*2. Methods Involving Chemical Reactions.*—As early as 1824, Prout demonstrated the presence of HCl in the gastric juice and devised a method for its measurement by determining the Cl. He differentiated that portion which was fixed to bases from that which was free in the acid. Reisner (1903) returned to this original principle. In the meantime, Hayem and Winter, and Martius and Lüttke, determined the total chlorides, making no correction for the neutral salts.

Bidder and Schmidt (1852) determined the K, Na, Ca, NH<sub>4</sub> and Cl, and subtracted the value of the neutral salts.

Sjörquist (1889) fused the stomach contents with BaCO<sub>3</sub>, which converts the Cl attached to acid into BaCl<sub>2</sub>. This is extracted with hot water, acidified and precipitated as BaSO<sub>4</sub> by sulphuric acid. From the weight of the BaSO<sub>4</sub> the amount of HCl is calculated. More than half a dozen modifications of this method have been proposed, in all of which the principle of fusion with BaCO<sub>3</sub> is employed.

All of the chemical methods determine the total HCl value, from which the free HCl must be subtracted to give the combined acidity.

*3. Hydrogen-Ion Concentration Methods.*—By measuring the hydrogen-ion concentration, one measures the true acidity. The two methods are: (1) The electrometric, and (2) the colorimetric. Both have been used by Michaelis and Davidsohn (1910) for those contents in which free HCl was present, and also for those in which there was no free HCl.

#### DISCUSSION

Contents which show free HCl require different consideration from those which do not, and will be discussed separately.

*1. Free HCl Present.*—(a) In titration of contents which show free HCl the combined acid can be estimated only after the free HCl has been neutralized. If there is an error in the determination of the free HCl, an error will exist also in the determination of the combined acid. Töpfer's indicator gives too high results for free HCl and hence must necessarily give too low values for combined acid. True neutrality, pH 7.0, has been the end point sought in titration methods. From what is now known of the nature of solutions and the end points of indicators, it is evident that phenol-phthalein is not an ideal indicator. Its end point is about pH 8.3-10.0, or 25-1000 times as alkaline as true neutrality. Christiansen (1912) has reviewed the methods for determining the combined acidity of stomach contents. He comes to the conclusion that phenol-phthalein gives results that are too high, and that correct results are obtained by litmus.

(b) The chemical methods are of great interest in determining the total HCl value. They were not considered important, because of the presence of other acids in the stomach contents. However, Boas (1894) showed that organic acids

seldom occur. Tobora (1905) showed that acid salts, such as phosphates, are negligible. NH<sub>3</sub> which is combined with HCl is not sufficient to be important. Martius (1892) showed that titration with phenol-phthalein gives results comparable to Lüttke's for the combined HCl. Lüttke's method does not, however, differentiate the Cl of HCl from that of neutral salts. When this is done, as in Prout's or in Bidder and Schmidt's method, the values obtained by the determination of the HCl are comparable to values obtained by titration with litmus. Christiansen found that titrations with litmus agree very well with Sjörquist's values when corrections for the NH<sub>4</sub>Cl are made. The combined HCl and the combined acid are therefore practically equivalent.

(c) Measurement of the hydrogen-ion concentration, in stomach contents showing free HCl, gives only the value of the free HCl. It supplies no information as to the combined acid.

*2. No Free HCl Present.*—(a) In cases which show no free HCl, titration gives a value comparable to the combined acid only when one takes the sum of the acid deficit and the total acid. If one uses the same indicators as for contents showing free HCl, the same errors will obtain. For one must titrate to two end points; for example, that of Töpfer's indicator for the acid deficit and that of phenol-phthalein for the total acidity.

(b) Methods involving chemical reactions give only the value of the HCl present. They give no information as to the acid deficit and hence can give no value for the potential combined acid.

(c) Methods for measuring the hydrogen-ion concentration give values that range from pH 3.0 to alkalinity, about pH 8.0. The electrometric method gives the reaction accurately. For approximate values, the colorimetric method of Michaelis and Davidsohn leaves little to be desired. In adult gastric contents with no free HCl, the pH is not an important factor, for no significant peptic digestion takes place until free acid is present. Measurement of the true acidity gives no information concerning the amount of acid necessary to bring the contents to neutrality or the amount of acid which must be added before digestion can progress.

#### BUFFER VALUE

*1. Definition.*—Buffer solutions are those to which acid or alkali can be added without causing a marked change in the reaction. They possess this property because they are either weak acids which on the addition of an alkali do not become alkaline until all the acid has been neutralized, or they are salts of weak acids which on the addition of acids do not become acid until the weak acid has been freed from its salt. In stomach contents the protein present acts as a buffer. It can combine with either acid or base, and give nearly neutral compounds. The amount of acid or alkali which can be added before the reaction reaches a definite acidity or alkalinity is called the buffer value. The amount of acid or alkali necessary to change the reaction from one hydrogen-ion concentration to another is the buffer value between those acidities. The total buffer

value is the amount necessary to change the reaction from pH 3.0, no free HCl, to pH 11.0, free alkali.

Fr. Volhard (1903) was the first to show that, in stomach contents, titrations with phenol-phthalein give higher values than those with litmus, because it is an indicator for alkaline solutions, and more alkali must be added to reach the end point. He also showed that this is due to the buffer action of the protein in the contents. What one really determines by titration methods is the buffer value to the end points of the indicators.

*2. Factors Affecting the Buffer Value.*—(a) *Concentration.*—Concerning the buffer values after different test meals, interesting problems arise. In general, one may say that the buffer value is not related to the hydrogen-ion concentration, but the hydrogen-ion concentration to the buffer value. The more concentrated the buffer solution, the greater is the amount of acid necessary to change the solution to a desired pH. For example, if there are two solutions of 100 c.c. of alkaline phosphate, the first normal and the second deci-normal, and 10 c.c. of normal HCl are added to each, the first will be alkaline, pH 8.0, and the second acid, pH 4.5. This is a difference in the hydrogen-ion concentration of more than a thousandfold. Therefore, a given amount of HCl secreted by the stomach yields with different foods widely different reactions.

(b) *Hydrolysis of Protein.*—What happens to the buffer value during peptic digestion is clearly indicated by the researches of Christiansen (1912). As digestion progresses the proteins become hydrolyzed or split into polypeptides or peptones, thereby producing more free alkaline groups. These combine with more HCl, thus reducing the hydrogen-ion concentration and free HCl, and increasing the buffer value.

(c) *Other Factors.*—Extraneous buffers, among which may be carbonates regurgitated from the duodenum, blood, foreign protein or phosphates, also increase the buffer value of the contents. If less water is present, the contents are more concentrated, and the apparent buffer value of the contents is increased.

*3. Significance of Buffer Value.*—To determine accurately the amount of alkali necessary to bring a sample of contents to true neutrality has no physiological significance. Such a determination merely shows the buffer value to pH 7.0; it does not show the acid secreted by the glands of the stomach nor the amount of alkali which the body must furnish to bring the contents to the reaction of the blood.

In order to measure the amount of HCl which the stomach secretes, one must first know whether any portion of the acid has been neutralized by the alkaline duodenal contents; moreover, one must know the true acidity of the food. Bread has an average reaction of pH 5.0, but may vary greatly (Henderson and others, 1919). For example, if the bread is pH 5.0 and the stomach contents also are pH 5.0, no acid has been secreted, and we have a case of true anacidity. Yet the titration as commonly carried out will show a considerable amount of combined acid. If the bread is pH 8.0 and the stomach con-

tents are pH 5.0, the titration represents only a portion of the acid which the stomach has secreted.

One may determine the amount of alkali necessary to bring the contents to the reaction of the blood, pH 7.4. Henderson and Palmer (1914) used this principle in determining the acidity of urine to show the amount of acid which the body had excreted in forming the urine. In the case of stomach contents, since one must examine only a sample of the total amount, the determination is quantitatively less accurate.

#### METHOD

The following method was devised to determine the buffer value of the contents. We shall describe: (1) Principle; (2) material; (3) indicator; (4) procedure; (5) results.

*1. Principle.*—To find the buffer value of a sample of stomach contents, one must determine the amount of acid or alkali necessary to change its reaction from pH 3.0 (no free HCl) to pH 9.6 (near the point of free alkali).

*2. Material.*—The material was the filtered or centrifuged contents recovered after an Ewald test meal of 25 grams of bread and 250 c.c. of water. The same material was used for the determination of free HCl.

*3. Indicator.*—Thymol-sulphon-phthalein .2 per cent in 95 per cent alcohol was used (Clark and Lubs (1917)). This is the same indicator that was used for the determination of free HCl. It determines both the free HCl and the buffer value of gastric contents, for it has an acid color zone red, pH 1.2-3.0; a neutral color zone yellow, pH 3.0-8.0; and an alkaline color zone green to blue, pH 8.0-9.6. The end point of phenol-phthalein is pH 8.3-10.0, and of thousandth normal alkali pH 11.1. Therefore, thymol-sulphon-phthalein gives nearly the total buffer value from free HCl to free alkali, and gives results similar to those with phenol-phthalein.

*4. Procedure.*—A. *When Free HCl is Present.*—(1) Add one drop, or .02 c.c., of .2 per cent thymol-sulphon-phthalein in alcoholic solution for each cubic centimeter of stomach contents. Titrate with .1 N NaOH free from carbonate to the full blue color of the indicator. Subtract the value of the free HCl found by the colorimetric method from the titration value.

#### Example.—

2 c.c. of contents neutralize 1.04 c.c. .1 N NaOH. Therefore, 100 c.c. neutralize 52 c.c. .1 N NaOH. Free HCl by the colorimetric method is 24 c.c. .1 N per 100 c.c. Therefore, 52 c.c. minus 24 c.c. equals 28 c.c. .1 N HCl, the buffer value per 100 c.c. of stomach contents.

(2) Instead of the colorimetric method for free HCl, direct titration to pH 3.0 may be made, thymol-sulphon-phthalein being used as the indicator. From this point the buffer value may be titrated directly.

B. *When no Free HCl is Present.*—(a) Add one drop of .2 per cent thymol-sulphon-phthalein for each cubic centimeter of stomach contents. Either of two procedures may then be followed to determine the acid deficit: (1) Titrate with .05 N HCl until HCl is just present, pH 3.0.

**Example.—**

.48 c. e. .05 N HCl required for 2 c. e. of contents.  
 .24 c. e. .05 N HCl required for 1 c. e. of contents.  
 .12 c. e. .1 N HCl required for 1 c. e. of contents.  
 12. c. e. .1 N HCl required for 100 c. e. of contents. Acid deficit.

(2) Add 1 c. e. of .05 N HCl and one drop of .2 per cent thymol-sulphon-phthalein. Read the value of the free HCl by the colorimetric method. Multiply this value by the number of cubic centimeters present (stomach contents plus acid), and subtract the product from 50 c. e. which is the value of the HCl added.

**Examples.—**

(1) 1 c. e. of .05 N HCl added to 2 c. e. of contents:  
 Free HCl colorimetric = 13 c. e. .1 N HCl. 50 c. e. Amount added.  
 Number of c. e. of sol. 3 39 c. e. Amount free.

Total amount free 39 c. e. 11 c. e. Acid deficit.

(2) 1 c. e. of .05 N HCl added to 1 c. e. of contents:  
 Free HCl colorimetric = 20 c. e. .1 N HCl. 50 c. e. Amount added.  
 Number of c. e. of sol. 2 40 c. e. Amount free.

Total amount free 40 c. e. 10 c. e. Acid deficit.

(3) 1 c. e. of .05 N HCl added to 4 c. e. of contents:  
 Free HCl colorimetric = 8 c. e. .1 N HCl. 50 c. e. Amount added.  
 Number of c. e. of sol. 5 40 c. e. Amount free.

Total amount free 40 c. e. 10 c. e. Acid deficit.

(b) To the acid deficit obtained in either of the ways given above, add the alkaline titration value. To obtain this, titrate (it is best to use another sample) with .2 per cent thymol-sulphon-phthalein as the indicator. Add .1 N NaOH free from carbonate until the full blue color is present. The sum of these two values gives the buffer value.

**Examples.—**

Acid deficit ..... 10 c. e. .1 N solution per 100 c. e. of contents  
 Alkali titration ..... 14 c. e. .1 N solution per 100 c. e. of contents

Buffer value ..... 24 c. e. .1 N solution per 100 c. e. of contents

**C. Discussion.**—Thus with the first procedure for the acid deficit, the titration is more difficult and the calculation simple. With the second, the procedure is simple and the calculation longer. It is not necessary to use .05 N HCl for the titration. Provided the proper calculation is made, amounts of HCl other than 1 c. e. can be substituted. The second procedure is given so that the acid deficit may be determined when one does not desire to determine the buffer value or when no microburettes are available. A similar method may be devised to determine without microburettes the power of the contents to combine with base. Other amounts of contents can be used. Equally good results are obtained with 10 c. e. samples and an ordinary burette.

Alkali free from carbonate is essential, for if carbonate is present it acts as a buffer and higher results are obtained. Carbonate-free alkali can be prepared by making a saturated solution of NaOH, allowing the carbonate to settle out, decanting the clear solution and diluting to the desired strength with freshly boiled hot distilled water. Solutions after being made must be protected from the air by soda-lime tubes.

**5. Results.**—The results in cases showing free HCl are shown in Table 1. Column 1 gives the buffer value with thymol-sulphon-phthalein. Column 2 gives the combined

TABLE 1  
CASES SHOWING FREE HCl

	Buffer value	Combined acid		Buffer value	Combined acid		Buffer value	Combined acid
1.	22	20	15.	49	39	29.	48	50
2.	31.5	26	16.	39	27.5	30.	43	30
3.	34	26	17.	24	14.5	31.	31	22
4.	26	18	18.	24	15	32.	31.5	27
5.	17	12.5	19.	26	20.5	33.	22	18
6.	25.5	19	20.	32	27	34.	15	13
7.	25	32	21.	11	10	35.	48.5	39.5
8.	16	11	22.	35	35	36.	15	13.7
9.	30	18	23.	24	17	37.	36	31
10.	17	20	24.	13	12.5	38.	23	21.5
11.	24.5	21	25.	19	22	39.	53	44
12.	31	25.5	26.	25	21	40.	25	20
13.	24	18	27.	26	25	41.	25	13.5
14.	30	23	28.	46	40			

Values are given in cubic centimeters of .1 N solution per 100 c. e. of stomach contents.

acid with Töpfer's indicator and phenol-phthalein. The values were obtained by subtracting the values of the free HCl from the total alkali titration. The results in cases showing no free HCl are shown in Table 2. Column 1 gives the acid

TABLE 2  
CASES SHOWING NO FREE HCl

	Acid deficit	Alkali value	Buffer value	Total acidity
1.	16	15	31	15
2.	10	12	22	11.5
3.	15	15.5	31.5	17
4.	6	22	28	20
5.	21	10	31	10
6.	1	30	31	22
7.	1	60	61	60
8.	6	18.5	24.5	24.5
9.	9	22	31	22

Values are given in terms of cubic centimeters of .1 N solution per 100 c. e. of stomach contents.

deficit with thymol-sulphon-phthalein. Column 2 gives the alkali titration with thymol-sulphon-phthalein. Column 3 gives the sum of these two values, the buffer value; the last

column gives the value of the total acidity with phenolphthalein. The buffer value in cases showing free HCl varies between 11 c. c. and 53 c. c. and in cases showing no free HCl varies between 22 c. c. and 61 c. c.

The values for the combined acid average 23.4 c. c.; the buffer value with thymol-sulphon-phthalein averages 28.3 c. c. The value for the total acidity averages 47.6 c. c.; the value for free HCl plus buffer averages 48.3 c. c. Thus the difference between the combined acidity and the buffer value is due largely to the value for free HCl with Töpfer's indicator, which is known to give too high values. If one subtracts the value of free HCl obtained by the colorimetric method from that of the total acidity obtained with phenol-phthalein, and compares the remainder with the buffer value, expressing all the values in terms of .1 N acid per 100 c. c. of stomach contents, one obtains the following: Total acidity, 47.6 c. c., minus free HCl, 20.0 c. c., equals combined acid, 27.6 c. c. The buffer value is 28.3 c. c. The buffer value in cases showing no free HCl averages 32.3 c. c.

*Discussion.*—The buffer value and the combined acid value, though almost equal in numerical terms, differ greatly in significance. The combined acid value signifies the amount of HCl united to the protein. The buffer value represents the amount of acid or base required to bring about a definite change in reaction. The buffer value by our method is lower than that which would be obtained by titrating with another indicator to pH 11.0; but the important factor is to determine the buffer value between any two known points. The method proposed determines neither the acid production nor the acid value of the stomach contents, nor the amount of alkali necessary to bring the contents to the alkalinity of the blood. By measuring also the acidity of the food, however, these three factors can be determined from the buffer value to certain end points—to the reaction of the food for the acid secretion, to pH 7.0 for the acid value of the contents and to pH 7.4 for the amount of alkali necessary to bring the contents to the reaction of the blood. The clinical conditions, in which the buffer value of the contents is a factor cannot be discussed here; but they are important and the buffer value throws some light on their solutions. The method here presented determines the buffer value.

#### SUMMARY

1. A method is proposed to determine the buffer value of stomach contents by titration, using thymol-sulphon-phthalein as an indicator.

2. This indicator changes from red to yellow at pH 3.0, "no free HCl," and from green to blue at pH 8.0-9.6, near the point of free alkali. This range of the indicator gives practically the total buffer value of the protein.

3. The procedure in cases showing free HCl is: Add 1 drop or .02 c. c. of .2 per cent thymol-sulphon-phthalein in alcoholic solution for each cubic centimeter of stomach contents. Titrate with .1 N NaOH free from carbonate, to the full blue color of the indicator. Subtract the value of the free HCl obtained by the colorimetric method from the titration value.

4. The procedure in cases showing no free HCl is: Add 1 drop or .02 c. c. of .2 per cent thymol-sulphon-phthalein in alcohol for each cubic centimeter of stomach contents. First titrate the acid deficit by adding .05 N HCl until the orange color appears; or, add 1 c. c. of .05 N HCl and determine the excess by the colorimetric method. In a second sample titrate with .1 N NaOH free from carbonates and thymol-sulphon-phthalein to pH 0.6, the full blue color of the indicator. The sum of the acid deficit and the alkali value equals the buffer value.

5. In cases showing free HCl, the buffer value is nearly equal to the value of the combined acid, or in cases showing no free HCl to the sum of the acid deficit and the total acidity.

6. Determination of the buffer value can be used to determine the amount of HCl secreted by the stomach, the acid value of the contents and the amount of alkali which the body must furnish to neutralize the stomach contents.

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#### MINUTE ON THE DEATH OF SIR WILLIAM OSLER

On motion of the Executive Committee of the Federation of American Societies for Experimental Biology in Cincinnati December 30, 1919, the following minute was drafted by Dr. C. H. Bunting of the committee:

In the death of Dr. Osler, the medical profession has suffered an immeasurable loss. Belonging to no cult, or age, or clime, but descended in direct line from Hippocrates, he was Master of the Art of Medicine in its purest form. As a teacher, he was again Master, painting with broad strokes pictures of disease never to be forgotten by the student. An investigator and an inspirer of investigation, a worthy counsellor of brother physicians, a deliver into the history of medicine, and an ornament to its letters; and withal so human and of such rare personal charm as to be beloved of all who came in contact with him. Such was the man we mourn.

We grieve not only for the loss of leader and friend, but also that death overtook him in the very shadow of the great conflict which had brought him so great personal loss and sorrow and robbed him of the mellow years which were so fully his due.

C. H. BUNTING,  
HENRY A. CHRISTIAN,  
A. S. LOEVENHART,  
*Committee.*

## CONTRIBUTIONS TO PSYCHOPHARMACOLOGY\*

By DAVID I. MACHT

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### INTRODUCTORY

The effect of drugs on psychological functions has been the subject of remarkably little investigation on the part of either psychologists or pharmacologists. Of course every medical man is familiar with some such phenomena; and every student is told of the delirifacient effects of belladonna, of the xanthopsia following the administration of santonin, and of the deafness and ringing in the ears produced by quinin and salicylates. When we, however, examine the literature, it is surprising to find how few experimental contributions on the subject have been made. Only two drugs have received any adequate consideration in this respect; they are alcohol and caffeine. The elaborate and exhaustive studies on alcohol by Benedict and Dodge<sup>1</sup> and others, and on caffeine by Dietl and Vintschgau<sup>2</sup>, and more recently by Hollingsworth<sup>3</sup>, are most valuable contributions dealing with the effects of these drugs. Other drugs which have received some consideration in this connection in recent years are the bromides, as exemplified by the work of Loewald<sup>4</sup>; strychnin, as studied by Poffenberger<sup>5</sup> and Lashley<sup>6</sup>; and in some experiments performed by Münsterberg<sup>7</sup>. The number of contributions to the domain of what we may be permitted to call "psychopharmacology" is certainly very meagre, as compared with experimental investigations on the action of drugs along other lines. During the past five years or so the author, with the assistance of a number of collaborators, has been interested in the subject, and it is proposed to sketch briefly in this paper some of the investigations carried out by him more or less jointly in the pharmaceutical and psychological laboratories of this university.

### I. A QUANTITATIVE STUDY OF ANALGESIA PRODUCED BY OPIUM ALKALOIDS

Opium and some of its alkaloids find their most extensive application in therapeutics in the relief of pain. The comparative efficiency of morphin, codein, papaverin and opium itself in respect to their analgesic powers has, however, never been experimentally investigated, and all our knowledge on the subject has been derived from clinical data. It is, therefore, not surprising to find a great diversity of opinion among various authors in regard to the pain-relieving properties of these drugs. Thus, Claude Bernard<sup>8</sup> regarded narcine, an inert substance according to the majority of investigators, as a powerful narcotic; again, Fronmüller<sup>9</sup> ranked narcotin in activity as next to morphin; while Baxt<sup>10</sup> extolled the wonderful pain-relieving virtues of papaverin. In conjunction with Drs. N. B. Herman and Charles S. Levy the author undertook an investigation of the comparative value of the above drugs

by studying their effect upon the sensory threshold for pain on various parts of the skin and mucous membranes.

In our experiments we have made use of a large Baltzer inductorium for producing quickly and conveniently finely graded pain stimuli. Having standardized our apparatus with the help of Dr. C. W. Hewlett, of the Physical Laboratory of this university, we were able to express the values of these stimuli, quantitatively, in henries or C. G. S. units, and in this way compare the strengths of the stimuli required to produce pain under various conditions.

The first step in the investigation was to determine whether a sufficiently constant pain threshold could be established. Martin<sup>11</sup> and his co-workers have studied the threshold of electrocutaneous sensation with the induction current, by dipping a finger in a liquid electrode, and have found that a definite sensory threshold can be established, subject to physiological, diurnal, nocturnal, and fatigue variations. Furthermore, Martin, Grace and McGuire<sup>12</sup>, in the only pharmacological study by this method, have found a definite lowering of the sensory threshold after the administration of acetphenetidin by mouth.

In our work we have made use of fine platinum electrodes, studying the effect of the induced current on individual pain points or groups of pain points in four different regions of the body. In this way our chances of error were lowered fourfold. The points most convenient for study employed by us were the skin on the back of the hand between thumb and forefinger, the tip of the nose, the tip of the tongue, and the lips.

In complete agreement with the localization of pain points on the surface of the body, as described by von Frey<sup>13</sup> and others, we have found that at any given spot of the body a definite pain sensation can be elicited by changes in mutual inductance of sufficient intensity, and that for every group of pain-points a pain sensation of exactly the same quality and intensity can be elicited by exactly the same intensity of electrical stimulus. By practice we were able to distinguish changes in pain sensation produced by moving the secondary towards or away from the primary coil a distance of not more than 0.1 cm.

Through numerous observations it was established that the normal pain threshold remains surprisingly constant for many hours in succession, and, through a series of other experiments, lasting over 25 hours each, the diurnal and nocturnal variations were found to be very slight.

Having determined the normal pain threshold in any given experiment, a drug was administered by subcutaneous or intramuscular injection, and after its absorption repeated readings were made. In this way a rise or fall in the pain threshold, or an analgesic or hyperalgesic effect, respectively, was detected and measured.

\* Read before The Johns Hopkins Hospital Medical Society, February 16, 1920.

Being fully aware of the fact that certain subjective elements, inherent in the character of the investigation, entered into our experiments, we have taken all possible precautions to eliminate errors arising from this source, and have made numerous control experiments.

Each experiment was carried out in the same room, and under perfectly constant conditions. Readings were always taken with the subject in the same position, and the subject was never allowed to look at the apparatus, but sat either with the eyes closed or fixed on some distant point. The electrodes employed were of course the same in any one experiment; the distance between the electrodes was kept fixed; the pressure with which they were applied to the surfaces was kept constant; the direction of their application was the same; and the wetness of the surfaces stimulated was maintained the same as nearly as could be judged.

When a drug was administered the subject was ignorant of its nature. Furthermore, as controls, normal saline and other inactive substances were often substituted in place of the drug without the subject's knowledge. It may be remarked in passing that, owing to the conflicting experiences of previous observers, we could not know the true pharmacological action of most of the alkaloids studied, thus further eliminating any subjective bias.

*Action of Opium Alkaloids Individually.*—By the above methods the six principal opium alkaloids, morphin, papaverin, codein, narcotin, narcein and thebain were studied. Administered in moderate therapeutic doses, it was found that in respect to their analgesic power, beginning with the strongest and ending with the weakest, they ranged themselves in the following order: Morphin (10 mgs.) → papaverin (40 mgs.) ← codein (20 mgs.) → narcotin (30 mgs.) → narcein (10 mgs.) → thebain (10 mgs.).

In respect to morphin in one of us an idiosyncrasy was noted. The subject (N. B. H.) was rendered hypersensitive to pain, and this effect could be measured quantitatively. This was an interesting confirmation of the existence of undoubtedly cases of persons who are not relieved by morphin but are rendered even more sensitive by it.

*Action of Combinations of Alkaloids.*—After a study of the individual alkaloids, the action of combinations of morphin and narcotin meconates (narcophin) and other salts was studied. It was found that a given dose of narcophin has greater analgesic power than is represented by the arithmetical sum of the effect of its constituents, morphin and narcotin. Thus, 5 mgs. of narcophin produces distinct analgesia, while 5 mgs. of morphin alone, or 10 mgs. of narcotin alone, produces no such effect. This observation is in complete agreement with Straub's<sup>14</sup> views on the synergism of these two substances. A similar action was observed with a mixture of the total opium alkaloids (pantopon). The full data appear in the *Journal of Pharmacology and Experimental Therapeutics*, 1916, VIII, 1.

## II. CONCERNING THE PERIPHERAL ACTION OF OPIUM ALKALOIDS

As a rule the analgesia produced by opium is, of course, of cerebral origin. Yet, we find a number of opium preparations, such as lotions, plasters, ointments, and suppositories, employed widely by clinicians for what is intended to be a local effect, and indeed some of these preparations are official in the U. S. P. and other pharmacopeias. While the opinion of many clinicians is that opium applied in this way exerts some local action without being absorbed into the system, the majority of modern pharmacologists ridicule this idea, and some go so far as to characterize this practice as a "pharmacological superstition."<sup>15</sup>

If we turn from mere belief or disbelief and speculation to scientific inquiry and experimental evidence on the subject, we find surprisingly few data upon which to base a rational and unbiased opinion. Indeed the few experimental data at our disposal do not at all disparage the local use of the drug.

It is well known, for instance, that dionin or ethyl morphin is a powerful anesthetic and has been used as such in ophthalmic surgery<sup>16</sup>; the same is true of benzoyl morphin or peronin. Moukhtar<sup>17</sup>, in an interesting experimental work on guinea-pigs, found that intradermal injections of minute quantities of solutions of opium alkaloids show a distinct local effect on the sensory nerve terminals, an effect which is not due to mechanical distension of tissue, as he proved by control injections of physiological saline solution. Even more interesting is the accidental discovery by Pal<sup>18</sup> of the locally anesthetic action of papaverin. On tasting a little papaverin sulphate he noted a numbness of the tongue. Further investigation by him showed that the alkaloid possesses marked local anesthetic properties, so that on applying it to a rabbit's eye a painless operation could be performed.

In order to clear up this perplexing question, experiments were carried out by the author in conjunction with Drs. H. J. Bollinger and S. L. Johnson. The method was the same as that employed in the previous research. The normal sensory threshold for pain on various parts of the skin and mucous membranes was determined by the electrocutaneous method. Various opium alkaloids were then applied locally for different periods of time, and the pain threshold was again determined.

It was found that the various opium alkaloids, when applied locally to the skin or mucous membranes, exert a distinct effect upon the sensory nerve endings, raising the sensory threshold as indicated by the greater amount of electrical stimulation required to produce the first sensation of pain. The most efficient in this respect was papaverin; next in order was narcotin; third came morphin; with narcein, codein, and thebain following in the order of their efficiency.

It was furthermore noted that a mixture of the total opium alkaloids (pantopon) exerted this effect even in a greater degree than the amount of morphin or papaverin which it contains would do if applied alone. From this it follows that the different alkaloids seem to potentiate each other, just as they

do when injected subcutaneously or intravenously and absorbed by the blood.

Without presuming to magnify its importance, it is evident, therefore, that opium, although primarily a central nervous poison, does also act to some extent upon peripheral structures, *i.e.*, sensory nerve endings, and that the empirical observations of the older clinicians, who advocated local applications of opiates for the relief of pain, are not totally without foundation. This would seem to be the more plausible if we bear in mind that in our experiments the time of application was purposely made as short as possible (generally from one to five minutes) on the one hand, while, on the other hand, the opium applications employed in clinical practice were allowed to remain in contact with the skin or mucous membranes over long periods of time. The complete data appear in the *Journal of Pharmacology and Experimental Therapeutics*, 1916, VIII, No. 8, August.

### III. ANALGESIA AFTER ANTI PYRETTICS

Inasmuch as the so-called antipyretic drugs produce also a distinct relief of pain in many conditions especially of a neuralgic character, it was interesting to inquire into their comparative efficiency. Accordingly, experiments were performed with the view of determining the pain threshold before and after administration of such drugs, in exactly the same way as had been done in the case of the opium alkaloids. This investigation has not yet been completed, but the author may say in this place that here too a lowering of the pain threshold was observed. Several antipyretics were studied and all of them were administered by mouth. It was found that acetanilid, acetphenetidin and pyramidon were especially effective in this respect. The results so far obtained indicate that the antipyretics, while not as powerful as the opiates, do also produce analgesia of the central origin, as shown by the change in the pain threshold after their administration.

### IV. ACTION OF OPIUM ALKALOIDS ON PSYCHOLOGICAL REACTION TIME

Following the studies on analgesia, an attempt was made to learn more about the effects of morphin and opium on the higher intellectual centers of the brain by means of observations on the reaction time before and after administration of those drugs. This investigation was conducted by the author, together with Captain S. Isaacs.

The experiments were made on the authors themselves and on ten colleagues, making twelve normal subjects in all.

The reaction time was measured by means of an improved chronoscope devised by Prof. Knight Dunlap, which is a far more accurate and convenient instrument than the old Hipp instrument. The apparatus is described by Professor Dunlap elsewhere.<sup>10</sup> It consists essentially of a synchronous motor, run on a tuning-fork vibrating fifty times per second, and registering the time in units of  $2\sigma$  or  $1/500$  of a second, the dial-hand of the chronoscope being controlled by an electro-magnetic clutch.

The simple sound reaction was obtained by the experimenter calling out a word or number into the speaking disc which started the chronoscope and the subject responding with a set answer as soon as possible through another speaking disc, thus stopping the clock. The results were then recorded in terms of  $2\sigma$  or  $1/500$  of a second. It is needless to state that the subject and experimenter were separated by a curtain in order to prevent their seeing each other.

The simple touch reaction was obtained in a similar manner. The experimenter touched the hand of the subject behind a curtain, the pressure of the touch starting the chronoscope going. The subject responded as soon as he perceived the touch sensation by pressing a bulb or touching a key which immediately stopped the clock.

The simple light reflex was tested by the experimenter pressing a key and thus lighting an incandescent lamp behind a white screen, the subject responding by pressing another key which extinguished the light and stopped the chronoscope.

In order to determine the more complex reaction time or association reaction time, various devices were tried, such as response to certain words (noun and adjective, subject and predicate, etc.), but none of those were found satisfactory for the purpose in view. The most convenient and satisfactory method was finally found to be the calculation of a mathematical problem. Two sets of problems were submitted to the subjects in all experiments. In one series the subject was requested to add 17 mentally to a two-figure number, and announce the sum as quickly as possible through a telephone arrangement which breaks the circuit and stops the clock. In the second series a more difficult task was given to the subject. The experimenter in this case announced a two-figure number and the subject was required to multiply the same by 3 and add 4 to the product, and then announce the result through the speaking disc, thus recording the reaction time.

In each test twenty numbers were generally employed at each sitting. This method furnished quite a complicated association test and at the same time eliminated as much as possible memory and habituation or familiarity. The subject in every case was expected to go through the mathematical process in his mind and not rely on his memory at all. Great attention was paid in the association tests to the number of errors made, and these were recorded for comparison of the normal reaction time with that obtained after the administration of the drug.

After the normal simple and complex reaction times had been established in any one experiment, the subject was given a drug by subcutaneous injection. The reaction times were then again measured in several series and the results tabulated and analyzed.

In testing simple reactions to sound, touch and light, the number of readings taken was generally from twenty to fifty or more in each series. In testing the association time, twenty problems were submitted by each method. An average reading was computed with the help of a calculating machine, thus saving an enormous amount of time, and the mean variations

were also computed by means of an adding machine, in accordance with Dunlap's method.<sup>20</sup>

Control experiments were occasionally made with injections of physiological saline solution, while the subject was under the impression that he was receiving a drug. It may be here stated that in such cases no definite change in the reaction time was noted.

It was found that the effect of a morphin injection depends on the size of the dose and manifests itself in one or more of three ways. In the first place, the absolute reading of the reaction may be affected. In the second place, the mean variations in the readings may be greatly increased or decreased. In the third place, in the case of association reactions, there may be an effect noted on the accuracy with which the subject performs mental problems.

After small doses of morphin (4-6 mgm.) there was noted a distinct *primary effect*, which consisted in a stimulation or a shortening of the reaction time, or in a decrease in the mean variation of the readings, or sometimes in both, and furthermore, in a lesser number of errors made in the computation of mathematical problems. This primary effect of morphin generally lasted half an hour or more and was followed by a secondary stage characterized by a depression, as indicated by the prolongation of the reaction time and greater variations in the readings or both. After very small doses of morphin, however, the depression was sometimes lacking.

After larger doses of morphin (8 to 15 mgm.), the primary stage of stimulation was very short and could be easily overlooked unless the readings were begun very soon after the injection of the drug. Depression, on the other hand, was the predominant picture, as could be seen by the prolongation of the reaction time readings and greater variations in the same, and also, in case of associations, by a greater number of mistakes.

Although the two stages of morphin action above described were not always marked, a careful analysis of all the experiments indicated that they were present in almost all the cases. The primary stage of quickening or stimulation, in our opinion, probably corresponds to the stage of *euphoria* or well-being so well known to the pharmacologist and which occurs after small doses of opiates. It is this euphoria or sense of well-being which probably is responsible in a great measure for the greater accuracy in mathematical calculations, especially in subject with a nervous temperament, inasmuch as the narcotic action of the drug is just sufficient to "take the edge off" the subject's anxiety. The primary stage of increased efficiency noted agrees well with the results of some other tests of mental efficiency produced by opium by mouth described by Münsterberg.

Three experiments were made with injections of narcotin hydrochloride alone. No definite change in the reaction time was produced by that drug.

Three experiments were made with a combination of morphin and narcotin in the ratio of one-to two, by administering the drug called narcophin, which is a mixture of morphin and

narcotin meconates. In two of the experiments there was a definite increase in narcosis and corresponding prolongation or depression of the reaction time noted as compared with morphin alone, being very marked in one case, but of a lesser degree in the other. In the third case the narcosis was, if anything, less than that produced by morphin alone.

Seven experiments were made with a combination of all the opium alkaloids in the form of pantopon, a mixture of hydrochlorides containing 50 per cent of morphin. In four of the experiments there was a very marked increase in narcosis and prolongation of the reaction time produced by pantopon as compared with that produced by the same amount of morphin when given alone. The deeper narcosis in these cases was also shown by the greater number of errors in the association problems. In two other cases the deeper narcosis was also present, but not in so marked degree as in the preceding two, and in one experiment the result was doubtful.

On analyzing all the experiments with pantopon and narcophin, the results could be summarized as follows: Out of ten experiments five showed a marked increase in narcosis and prolongation of the reaction time; three experiments showed also a definite but not so marked a prolongation of the reaction time as compared with morphin alone; one subject gave doubtful results, although his accuracy was markedly affected in regard to association problems, and in one case the reaction time was quickened by the combination more than it was by morphin alone. It was also noted that in all experiments, both with morphin alone and with its combinations, the simple reactions were less affected by the drugs than the association tests, thus showing that the narcotics exerted their influence especially upon the higher functions of the brain. The complete data appear in *Psychobiology*, 1918, I, 327.

#### V. EFFECT OF SOME ANTIPYRETICS ON REACTION TIME

Having studied the effects of opium and morphin on simple and complex reaction times, it was interesting to inquire into the effect of the other great class of analgesic drugs, the antipyretics, on the same functions. Precisely the same method was employed in this research which was performed by the author in collaboration with Messrs. S. Isaacs and J. Greenberg. In this set of experiments, however, the drugs were given by mouth.

The experiments were performed for the most part on the authors themselves, and occasionally on other subjects. About forty experiments were made in all, each lasting from two to five or more hours. The drugs studied were the following: quinin, acetanilid, acetphenetidin (phenacetin), antipyrin, phenyl salicylate (salol), acetylsalicylic acid (aspirin), and pyramidon. In order to ascertain whether these drugs produced a synergistic effect or not, the following combinations were also studied: acetanilid and salol, phenacetin and salol, acetanilid and phenacetin, aspirin and salol, and antipyrin and aspirin. The doses of the drugs never exceeded those employed by conservative therapeutists.

A careful study and analysis of all the data obtained has led the authors to the following conclusions. The results obtained with antipyretics are quite different from those found after morphin or opium. No primary stage of stimulation or shortened reaction time was noted after administration of antipyretics, except possibly after small doses of quinin. It was found that in all cases the ordinary doses of antipyretics produced either very little effect on the reaction time, or if affecting it at all, they always impaired it as indicated by the prolongation of the mean readings, by the increase in the mean variations of readings, or by both. The most powerful or depressant drug in this respect was found to be pyramidon. This is not surprising, inasmuch as pyramidon in the author's (M.) experience and in the experience of many physicians is one of the most efficient analgesics—its effect coming closer to that of the narcotics than that of most other antipyretics. It was furthermore interesting to note that when the antipyretics exerted an influence on the reaction time, the simple reflexes or reactions to sound, light and touch were more prolonged or impaired than the more complex association tests. Of the three simple reactions that of touch was more generally retarded than those of sound or light. The association tests were also depressed or impaired, but usually in a distinctly lesser degree than the simple reactions or reflexes. Thus, for instance, the absolute readings in case of the mathematical calculations were sometimes even actually improved and the depressant effect of the drug revealed itself only through the greater numbers of errors committed.

Experiments with combinations of the various antipyretics gave results which could be explained by a simple summation or addition of the individual effects of the components. No so-called synergism or potentiation of one drug by another was observed.

The curious difference in the effect of the drugs on the simple reactions as compared with that on the more complex ones is the direct opposite of the results obtained after administration of opium or morphin. In the latter case, the simple reactions were always less impaired than the more complex association tests. A comparison of the findings obtained with the two groups of analgesics, the opiates or narcotics, and the antipyretic analgesics, seems to point to some lower synapse as the seat of action of the coal-tar derivatives. The full data appear in *Psychobiology*, 1917, I, 19.

#### VI. EFFECT OF ANTI PYRETICS ON THE NEUROMUSCULAR TEST OF "TAPPING"

This test consists briefly in the continuous tapping by the subject with a brass stylus upon a brass plate so adjusted that each tap or contact of the stylus on the brass plate is electrically registered on a counter. The number of taps made over a definite period of time is a rough index of the neuromuscular coördination of the muscles of the arm and hand. In the present investigation, observations were made upon the authors and occasionally on other subjects. The subject was required to tap continuously for three minutes at a time, and

the number of taps registered was noted at the end of each minute. Having noted the normal tapping in any one experiment, the subject was given an antipyretic by mouth and the test was repeated, generally about an hour later, but in some cases several readings were repeatedly taken at definite intervals. The effect of the following drugs was studied: Phenacetin, antipyrin, acetanilid, quinin sulphate, pyramidon, aspirin and salol. In addition to the study of individual drugs, the following combinations were also administered: Acetanilid plus phenacetin, 5 grains each; phenacetin plus salol, 2½ grains each and 5 grains each; aspirin and salol, 5 grains each; acetanilid and salol, 2½ grains each and 5 grains each and antipyrin and aspirin, 5 grains each. The results of the experiments were not very striking. Briefly, however, the effects of the drugs may be summarized as follows: Phenacetin, acetanilid, antipyrin and quinin in the ordinary doses (not exceeding 5 grains) showed a definite tendency to improve the tapping rate. Larger doses of these drugs (8 or more grains) tended to impair the efficiency in the test. The improvement after phenacetin and antipyrin was greater than that after acetanilid and quinin. After pyramidon, salol and aspirin, no definite change could be noted as the different subjects showed different results. Combinations of the various drugs studied all showed a tendency to improve the tapping rate. This was especially marked after the combinations of acetanilid and salol and phenacetin and salol. (See *Proceedings of Society for Experimental Biology and Medicine*, 1917, XV, 61-62.)

This investigation as well as the following was conducted by Drs. Macht, Isaacs and Greenberg.

#### VII. EFFECT OF OPIATES AND ANTI PYRETICS ON THE FIELD OF VISION

The same experimenters studied the influence of some opiates and antipyretics on the field of vision. Observations were made on the authors themselves and some of their colleagues with an ordinary perimeter, the field of vision being tested for four colors, white, blue, red and green.

It was found that the opiates, morphin and pantopon, taken by injection in every case produced a definite though very slight contraction of the field of vision. As between morphin and pantopon, little difference was noted, yet it may be well to state that in two out of three subjects, on whom the observations were made, the morphin injections seemed to produce a slightly greater limitation of the field of vision than pantopon.

Of the antipyretics studied it was found that they produced either no change in the field of vision at all or had a slight tendency to increase it. This was especially noted in the case of acetanilid, acetphenetidin, aspirin, and the combinations acetanilid plus salol and acetphenetidin plus salol, which in some of the experiments produced a definite though not marked increase in the field of vision. It was curious to note, furthermore, that the increase was especially apt to occur for

the white and blue colors, which ordinarily under normal conditions give the largest field of vision.

The conclusions drawn from all the observations are that the opiates, while producing but little effect upon the field of vision in the normal subject, when they do exert any influence, tend to narrow the field, whereas the antipyretics, when any effect is to be noted, tend to increase the field of vision. What mechanism it is that produces the positive findings in the different cases, it is difficult to say. At any rate, various factors, such as the constriction of the pupil in the case of opium, vasmotor changes produced by antipyretics, specific effects upon the retinal ganglia and nerves and central cerebral effects must be all considered. (See *Proceedings of Society for Experimental Biology and Medicine*, 1917, XV, 47-48.)

#### VIII. CONCERNING THE INFLUENCE OF ANTIPYRETICS ON THE ACUTY OF HEARING

While conducting the above experiments with antipyretics, the authors (Macht, Greenberg and Isaacs) made systematic observations on the effects of these drugs on hearing. The results were very interesting and unexpected. The experiments were performed on normal human subjects and in a few cases on persons suffering with mild deafness. The tests were made by means of a watch, in a quiet room, with the subject in a sitting position; and all necessary controls were carried out for the elimination of errors. In every experiment the normal limit of error was first determined; the drug to be studied was then administered by the mouth, and the acuity was afterwards tested at definite intervals of time. Only therapeutic doses of the drugs were administered. The following substances were studied: acetanilid, acetphenetidin, antipyrin, pyramidon, lactophenin, salol, aspirin, quinin, sodium salicylate, and "melubrin." After studying the effects of individual drugs, certain combinations were administered. The following were among the combinations studied: acetanilid plus sodium bicarbonate, acetphenetidin plus salol, acetanilid plus salol, acetanilid plus acetphenetidin, antipyrin plus aspirin, and antipyrin plus salol.

The results obtained were interesting and unexpected. It was found that some drugs decrease the acuity of hearing while others increase it. Furthermore, it was found that certain combinations of antipyretics produce synergistic effects not explainable by the simple arithmetical sum of the effects produced by the components individually. Among the agents found to decrease the acuity of hearing were acetanilid, salol and aspirin. Among those found to increase the hearing were antipyrin, pyramidon, and small doses of quinin. Among the most remarkable combinations studied were those of acetanilid plus sodium bicarbonate and acetanilid plus salol. It was established that whereas acetanilid given alone decreases the acuity of hearing, and ordinary doses of sodium bicarbonate given alone produce no change, a combination of the two produced a definite improvement in the acuity of auditory perception. Again, whereas acetanilid and salol, when administered separately, each by itself tended to impair the hearing,

a combination of the two actually increased the acuity of sound perception. The peculiar synergism of acetanilid with sodium bicarbonate recalls the experiments of Hale<sup>21</sup> who called attention to the fact that such a combination is less toxic for animals than the same dose of acetanilid given alone.

Complete data of this research, together with an attempt at an explanation of this peculiar synergism, appear in the *Journal of Pharmacology and Experimental Therapeutics*, 1920, XV, 1.

#### IX. EFFECT OF ANESTHETICS ON THE SUBSEQUENT BEHAVIOR OF RATS

During the past year or two the author, in conjunction with Dr. C. F. Mora, has been conducting psychopharmacological experiments on the behavior of albino rats. These experiments were performed by means of the circular maze, with camera lucida attachment invented by Prof. John B. Watson, of the Psychological Department of this university. In connection with these experiments, the authors are greatly indebted to Professor Watson for the apparatus as well as for valuable advice. The maze has been described by Professor Watson elsewhere.<sup>22</sup> By means of this apparatus one can study the rate of learning in albino rats and the effect of various factors on memory habit after they have learned the maze problem. The present authors studied the effects of various drugs on both of these. The effect of the general anesthetics, chloroform, ether and nitrous oxide, was investigated. It was found that the three anesthetics, chloroform was the most deleterious in its effects and for the subsequent behavior of the animals. The experiments were performed by first training rats so that they found their way through the maze by the shortest route and in the quickest time. After this habit was established the rats were anesthetized and their behavior was again noted, with especial reference to how soon they regained their normal intelligence after the anesthesia was over. It was found that after chloroform the rats were depressed a very long time. Their memory was impaired and it took quite a long time before they regained their previous agility. Ether did not produce much depression, unless administered for a very long time, and even after prolonged ether anesthesia the animals recovered more quickly than after chloroform. Nitrous oxide and oxygen anesthesia was the least depressing of the three. (See *Proceedings of Society for Experimental Biology and Medicine*, January, 1920.)

#### X. EFFECT OF OPIATES ON THE BEHAVIOR OF ALBINO RATS

The author and Dr. C. F. Mora have conducted an extensive investigation of the effect of opiates on the behavior of rats in the circular maze. About twenty rats were studied in this research; and the effect of the following drugs was noted: Morphin, codein, papaverin, narcotin, narcein, thebain, pantopon, and narcophin. In this research the effect of the opiate was studied on the behavior of the rats after training in the maze and not on the rate of learning. It was found that morphin, even in minute doses, markedly impaired the mem-

ory-habit and activity of the animals. Codein, in nine experiments out of eleven, produced a depression, and in two experiments, no change. Narcotin, in five experiments out of seven, was depressant, and in two experiments produced little or no change. Narcein, in six experiments out of ten, showed little or no effect, and in four experiments a slight depression. Thebain, in one experiment out of eleven, showed a stimulation, and in ten experiments, a retardation. The least depressant of the individual alkaloids was found to be papaverin, which produced depression only after very large doses, but otherwise had no effect. Out of all the morphin experiments, in one animal a primary excitation was noted after a small dose of the drug. The morphin combinations, pantopon and narcotin, in the majority of the experiments were found to be much less depressant than the corresponding doses of morphin alone in the same animals. It was very interesting to find that in all experiments, even where large doses of the narcotics were administered and produced marked and prolonged depression or impairment of the cerebral functions, the animals sooner or later all recovered their intellectual activities. This, of course, is very encouraging experimental evidence in connection with the clinical treatment of the opium or morphin habit. Full data will appear in the Journal of Pharmacology and Experimental Therapeutics.

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## A BIOLOGICAL STUDY OF HEMOLYTIC STREPTOCOCCI FROM THROATS OF PATIENTS SUFFERING FROM SCARLET FEVER. PRELIMINARY REPORT

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The relationship of *S. hemolyticus* to scarlet fever has long been the subject of controversy, certain investigators claiming for it an etiological rôle, while others maintain that the streptococcus found is probably a secondary invader, which might possibly be responsible for many of the common complications of scarlet fever, but is not the causative agent. Although *S. hemolyticus* is practically always found in the throats of individuals suffering from scarlet fever, yet marked variations in carbohydrate fermentation reactions and in the ordinary cultural differential tests favor the opinion that the streptococcus in these cases constitutes a heterogeneous group.

The development of a technic for the differentiation of hemolytic streptococci into groups by means of agglutination and protection experiments devised by Dochez, Avery and Lancefield<sup>1</sup> has made it possible to use this technic in the study of a series of strains of streptococcus isolated from the throats of patients with scarlet fever to determine whether or not there is any biological relationship among the organisms

studied. A study has been made of 25 strains of *S. hemolyticus* isolated from as many cases of scarlet fever, for the most part during the first week of the disease when the majority of throats showed the hemolytic streptococcus as the predominating organism. Control tests were carried out at the same time with hemolytic streptococci obtained from human sources in other pathological conditions, for example, tonsillitis, abscesses, septicemia, erysipelas. All organisms isolated were Gram positive streptococci of the type of *S. hemolyticus* with individual variations in size, length of chain, degree of hemolysis, morphology of colony and initial growth in broth—differential characteristics emphasized by some of the earlier investigators, but not peculiar to the streptococci of any particular pathological condition.

Agglutination tests were made following the technic of Dochez and Avery. The strains varied greatly in the diffuseness of growth in broth, but it was found that after several transfers in an optimal medium the suspensions usually became perfectly diffuse and were available for agglutination tests. Particular care in the preparation of the broth was necessary: Fresh beef, carefully freed from fat, infused in

<sup>1</sup> Dochez, A. R., Avery, O. T., and Lancefield, R. C., J. Exp. Med., 1919, XXXI, 179.

TABLE I

Scarlatinal streptococcus strains	Antistreptococcal sera									
	Non-scarlatinal					Scarlatinal				
	Type S3	Type S23	Type S32	Type S60	Type S84	Type S273	23	24	25	
11	—	—	—	—	—	+++++	++++	++++	++++	
12	—	—	—	—	—	++++	++++	++++	++++	
13	—	—	—	—	++++	+++	+++	+++	+++	
14	—	—	—	—	++++	++	++++	++++	+++	
15	—	—	—	—	—	+++++	++++	++++	++++	
16	—	—	—	—	+++++	+++++	+++++	++++	++++	
20	—	—	—	—	—	—	—	—	—	
23	—	—	—	—	—	+++	+++++	+++	++++++	
24	—	—	—	—	—	+++	+++++	+++++	+++++	
25	—	—	—	—	+++++	+++++	+++++	++++	++++	
26	—	—	—	—	—	—	—	—	—	
27	—	—	—	—	—	+++	+++	+++	+++	
28	—	—	—	—	—	+++	+++	++++	++++	
29	—	—	—	—	—	+++	+++	++++	++++	
35	—	—	—	—	—	+++	+++	+++	++	
36	—	—	—	—	—	—	—	—	—	
38	—	—	—	—	—	+++++	++++	++++	++++	
39	—	—	—	—	—	+++++	++++	++++	++++	
45	—	—	—	—	—	—	—	—	—	
47	—	—	—	—	++++	+++++	+++	+++++	++++	
50	—	—	—	—	+++++	+++++	++++	++++	++++	
53	—	—	—	—	—	+++++	++++	++++	++++	
54	++++++	—	—	—	—	+++	+++	++++	+++	
56	—	—	—	—	—	+++	+++	++++	+++	
S 273	—	—	—	—	—	+++++	+++++	+++	++++	

+ indicates agglutination present in a dilution of 1:20; ++ 1:40; +++ 1:80; +++++ 1:160; ++++++ 1:320; +++++++ 1:640; ++++++++ 1:1280;  
+++++ 1:2560. The minus sign (—) indicates no agglutination.

TABLE II

Non-scarlatinal streptococcus strains	Antistreptococcal sera							
	Non-scarlatinal			Scarlatinal				
	Type S60	Type S273	24	25	Non-scarlatinal streptococcus strains	Non-scarlatinal	Scarlatinal	
4	—	—	—	—	32	—	++	—
5	—	—	—	—	37	—	—	+
6	—	—	—	—	40	+	—	—
9	—	—	—	—	41	—	—	—
10	—	++++	++++	++++	49	—	—	—
21	—	—	+	—	55	—	++++	++++
22	—	—	—	—	57	—	++++	++++
31	—	—	—	—	58	—	—	—
					59	—	—	—

distilled water, was used, made up in the customary manner, with the addition of dibasic potassium phosphate as buffer, adjusting the reaction to a pH of 7.8 before fractional sterilization in the Arnold, so that the final reading after sterilization was approximately 7.5. Even with this medium it was necessary in the case of certain strains to pass them through several generations in glucose broth in order to get them diffuse, or even through blood or ascitic broth. In the agglutination tests fresh 18- to 24-hour broth cultures were used, 0.3 c. c. to each tube, to which were added equal parts of the serum to be tested in a final dilution of from 1 to 20 to 1 to 640 (in some cases 1 to 2560) with a normal serum control for each dilution and a control in broth set up at the same time. The serum dilutions were made in broth of the same lot as that used for the bacterial suspensions. It was not found necessary to wash and resuspend the cultures as Dochez and Avery recommend. The mixtures were incubated in the water-bath at 56° C. for one hour, after which readings were made.

It will be recalled that in the work of Dochez and Avery, carried out principally with hemolytic streptococci from measles and various respiratory infections, 68 per cent of the strains were differentiated into four definite types: the so-called Type S3, Type S23, Type S60 and Type S84. Subsequently they have added two other groups: Type S32 and Type S273. The type organisms used in making the specific sera for their agglutination tests were obtained from throat cultures from lobar pneumonia (S23), measles (S60), lung cultures from bronchopneumonia (S3 and S32), pleural fluid from bronchopneumonia (S84) and pus from a case of scarlet fever (S273).

In this preliminary series of agglutination experiments 25 hemolytic streptococcus strains of scarlatinal origin have been tested against these six antistreptococcal sera of Dochez and Avery, five of them of non-scarlatinal origin and one (Type S273) of scarlatinal origin, and in addition against three antistreptococcal rabbit sera prepared by immunization with three of the author's strains, namely, Nos. 23, 24 and 25. The condensed results are presented in the accompanying tables.

It will be noted in Table I that all strains isolated from throats of patients with scarlet fever, with the exception of Nos. 20, 26, 36, 45 and 54, were agglutinated by all four antistreptococcal sera made from strains isolated from patients with scarlet fever, in the majority of instances in as high dilution as the homologous strains. Inasmuch as in most cases only one colony was isolated from any particular throat culture, and in view of the fact that more than one strain of hemolytic streptococcus may be present in these throat cultures (as would be suggested by the presence of a Type 3 organism in No. 54 above), the five exceptions just noted may be due to having selected a colony of another type instead of an organism of this particular group. Furthermore, these same 20 strains failed to be agglutinated by any of the five antistreptococcal sera of non-scarlatinal origin, where rabbit sera were used that did not show a tendency to non-specific

agglutination of streptococci or where sheep sera were available. However, in the case of serum Type S84, which showed such a tendency to non-specific agglutination with six strains, no sheep serum has as yet been available.

In Table II it is seen that but three (Nos. 10, 55 and 57) of the 17 *S. hemolyticus* strains from sources other than scarlet fever were agglutinated by the three sera of scarlatinal origin used. These three deserve special consideration. No. 10 was from a case of acute tonsillitis in a patient who had been exposed to scarlet fever, but who did not develop an exanthem.

No. 55 was isolated from the pus from a mastoid during operation on a nurse who had entered the hospital one week previously with a severe sore throat, aching, general malaise, fever, followed by an acute suppurative otitis media and then an acute mastoiditis. This strain was found in pure culture in the pus from the mastoid at the time of operation and subcultures were agglutinated by the three antistreptococcal sera of scarlatinal origin. Three days after operation redness appeared about the site of the operating wound, which in the next 24 hours had spread over the entire face, neck, shoulders, axillæ, both arms, chest, back, abdomen, perineum and thighs, and then more slowly spread down to the ankles. The condition was diagnosed as erysipelas. Two weeks later extensive desquamation started, which has continued to date.

No. 57 was admitted to the isolation ward as a suspected case of scarlatina, at about the same time that several other nurses had developed scarlet fever. The patient was suffering with a severe sore throat, characterized by redness and swelling of tonsils and pharynx, without membrane formation, and with marked swelling and tenderness of the anterior cervical lymph glands, flushing of the face, neck and chest, but no generalized erythema.

One other fact was of some interest. All 25 streptococcus strains from patients with scarlet fever fermented both lactose and salicin (except Strain 36), 5 of the 25 also fermenting mannit, thus placing them in Holman's classes of *S. pyogenes* (20 strains) and *S. infrequens* (5 strains) respectively, and not in the group of *S. anginosus* where Holman placed most of his strains from various throat infections, including scarlet fever. This work would indicate, therefore, that the streptococci found in throat cultures in cases of scarlet fever do not fall in the anginosus group, but in the majority of instances in the pyogenes group.

#### CONCLUSIONS

1. In a study of 25 strains of *S. hemolyticus* isolated from the throats of patients with scarlet fever, 20 or 80 per cent were agglutinated by four different antistreptococcal sera made with streptococci isolated from scarlet fever cases.
2. None of these strains were agglutinated by five antistreptococcal sera of non-scarlatinal origin (except in the few instances noted).
3. But three of seventeen strains of non-scarlatinal origin were agglutinated by these three sera of scarlatinal origin, and

these three may have been either atypical scarlatinas or scarlatinatous contacts.

4. Certain differences in cultural characteristics, particularly in the fermentation of carbohydrates, were noted.

From this study, therefore, it would appear that a great majority (80 per cent) of strains of *S. hemolyticus* isolated from the throats of patients with scarlet fever belong to a specific biological type as determined by the reaction of agglutination. It is possible that the heterogeneous strains found may be accidental dwellers in the throat and that a more careful selection of colonies may reveal a still higher proportion of unit type organisms.

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## ADENOMATA OF THE CAROTID GLAND

By MONT R. REID

(From the Surgical Department of The Johns Hopkins Hospital)

Tumors of the carotid body have been studied by many authors. The recorded cases, however, are scarcely more than the number of authors who have written on the subject. Steindl, in 1915, published a carefully studied case and collected from the literature 41 others. Recently Reenstierna has reported two cases and found in the literature additional ones, bringing the total of reported cases to the number of 66.<sup>1</sup> Most authors have based their report on the observance of one case, 1 author on four cases, 2 on three cases and 3 on two cases.

From Professor Halsted's clinic three cases may be added to the list. Two of these were operated upon by myself; a specimen of the tumor in the remaining case was referred to me for diagnosis at the time I was assistant in the Department of General Pathology.

CASE 1.—(Surgical Nos. 31826 and 48031.) A white man, aged 46, was admitted to The Johns Hopkins Hospital March 28, 1913, complaining of a swelling in the left side of his neck. The family history was unimportant. In his past life he had had the usual diseases of childhood, including scarlet fever at the age of eight and typhoid fever at 18.

One morning in February, 1908, he accidentally discovered a small lump about midway between the angle of the jaw and the clavicle. He thought that it had appeared over night. Without causing any discomfort other than that of the disfigurement, the

lump gradually grew larger "in spite of all sorts of treatment"—drugs and local applications. Pulsation of the tumor was first observed in 1911 and had become much more pronounced in the two years before his admission. A few weeks before coming to The Johns Hopkins Hospital he was seen in Philadelphia by a surgeon who told him he had an aneurysm and advised him to see Dr. Halsted.

On his first admission to The Johns Hopkins Hospital, March 28, 1913, a diagnosis of carotid aneurysm was made by all of the many surgeons who examined the tumor. A large, expansile, pulsating mass involved the left side of the neck extending from the lobe of the ear to within 3 cm. of the clavicle, and from the middle of the neck anteriorly to the trapezius muscle posteriorly (Fig. 1). Its external circumference was 17 cm. The trachea was displaced 1 cm. to the right of the midline. A thrill was easily felt along the posterior part of the tumor. The mass was slightly compressible. Firm pressure below the tumor did not lessen the pulsation in it. There was a scarlatiniform flush over the upper part of the chest and the neck. There was expansile pulsation over the whole tumor. Careful examination of the eyes and eyelids revealed no evidence of disturbance of function of the cervical sympathetic nerves. Blood pressure 160. Dr. G. J. Heuer wrote: "The left wall of the pharynx is dislocated toward the median line, so that the left tonsil is pushed inward and lies directly in the median line just below the uvula. The entire wall of the pharynx pulsates visibly. The vocal cords can hardly be seen, but from a fleeting view both cords seem to be active." Wassermann, negative.

Operation, April 1, 1913, by Dr. Halsted. Ligation of the common carotid artery. It was observed that the carotid artery occupied a more lateral position than was normal. About it there were numerous dilated venules, suggesting an angioma. These venules bled easily. The artery was dilated and its wall was very soft. The bleeding from the angiomatic tissue made it necessary to

<sup>1</sup>This author excludes a few cases reported as carotid body tumors. Winslow refers to 72 cases; Schley to 76; and Lund to 80. The correctness of the diagnosis in several instances is questionable.

divide the sternomastoid muscle so that the artery could be ligated without lifting it from its bed. The omohyoid and platysma muscles were also divided. After ligation of the artery these muscles were sutured.

At the end of the operation there was no pulsation in the tumor.

April 6, 1913, it was noted that the tumor was much softer and more compressible. No pulsation. Its measurements had decreased 5 cm. A faint bruit, however, was audible. The temporal artery rapidly became much larger and tortuous.

April 21, 1913. Patient discharged. A faint bruit was present in one place. No pulsation. No thrill. The mass was smaller.

April 10, 1919. The patient returned because the tumor in his neck had gradually increased in size. The increase had been forward and laterally, and particularly in the lower part of the tumor. He had observed a return of pulsation soon after leaving the hospital, and this had gradually become more evident. The disfigurement caused by the tumor was his chief worry.

About two weeks after the operation in 1913, the vision of the left eye began to fail and in a period of six months to one year was entirely gone. In May, 1917, his eye was removed, the diagnosis of glaucoma having been made by the surgeon. Vision in the right eye remained good. His voice never became impaired.

When seen by me on April 11, 1919, I came to the conclusion that the condition was not a true arterial aneurysm, but probably an angiomatic tumor or an arterio-venous fistula. A huge swelling (Figs. 2, 3 and 4) involved the left side of the neck from the lobe of the ear and the mastoid process to the midline anteriorly and downward almost to the clavicle. The trachea was displaced 2 cm. to the right of the midline. The circumference of the tumor, vertically, was 15 cm.; transversely, 19.5 cm. The superficial temporal vessels were very prominent and tortuous. The pulse was equally well felt in them. Over the tumor and the upper part of the chest there was a diffuse erythematous flush of the skin. The face was suffused. The color of the entire body, but particularly of the face, suggested an abnormally dark pigmentation of the skin. Over the lower part of the tumor there were large, tortuous veins, suggesting an angiomatic condition. A slight heaving pulsation of the whole tumor was visible. This was better seen than felt, although on palpation the mass seemed to be definitely expansile. A diffuse thrill could be felt over the entire tumor but was most marked anteriorly and laterally. One could hear a continuous bruit with a systolic intensification of an almost musical character. On firm pressure the main mass was only slightly compressible. It was noted that palpation produced paroxysms of coughing. The large vessels running over the swelling could be felt as grooves in it. Many of these vessels were rather large, tortuous arteries. No pulsation in the left common carotid artery could be felt, and firm pressure over the region of this vessel did not affect the pulsation of the supposed aneurysm. Hearing was a little impaired in the left ear. The radial pulse was equal on both sides. Systolic blood-pressure, 134; diastolic, 94.

An examination by Dr. S. J. Crowe revealed a complete paralysis of the left vocal cord. *There was no bulging of the left side of the pharynx.* The tonsils occupied normal positions.

April 15, 1919. Operation by Dr. Mont Reid. The operation required 4 hours and 20 minutes and was unusually difficult on account of the extreme vascularity. Before any tissues could be divided it was necessary to apply clamps, for huge vessels were encountered everywhere. There were numerous vessels as large as the normal jugular vein. The carotid artery, which had been ligated at the first operation, was not recognized during this operation. It was necessary to resect a portion of the vagus nerve and the internal jugular vein. The 11th and 12th nerves ran directly through the tumor and had to be divided. The sternomastoid muscle was excised with the tumor.

At the completion of the operation we began to study the specimen which, by the time it was removed, we had thought might be

an angioma or angio-sarcoma instead of an aneurysm. On sectioning it we were surprised to see that we were dealing with an extremely vascular tumor, which had a beautiful coloring. The center of the tumor was yellowish-brown, whereas towards the periphery many areas were of an amber color. We were certain that we were dealing with a pigmented tumor. Dr. Halsted immediately suggested that the specimen was a tumor of the carotid body. I did not agree, for the frozen section looked exactly like a case of so-called perithelial angio-sarcoma that we had studied in the Pathological Department in 1914. After a brief study of the literature I learned that I was wrong, and as a result, the interesting case of vascular tumor of 1914 is included as Case 3 in this report.

For 36 hours after the operation the patient caused us some anxiety on account of œdema of the epiglottis which interfered with his breathing. After his convalescence was uneventful, except for the discomfort caused by the division of the hypoglossal and vagus nerves. His voice was not affected, for the left vocal cord was paralyzed before the operation. He left the hospital May 1, 1919, just 16 days after the operation. At that time (Fig. 5), the tortuous vessels were less prominent and the face and neck were much less suffused.

About one month after this patient left the hospital he was seen by Dr. Halsted who was quite surprised at the change in his appearance. The erythematous flush about the neck and the suffusion of the face were gone, the yellowish tinge had disappeared and the skin had taken on its normal color. The large tortuous temporal vessels were not evident.

The specimen of this case (Fig. 7) weighed 190 grams; measured 8.5 x 6.5 cm. Very large vessels ran through the tumor. The coloring and general appearance of the cross-sections were typical of the numerous descriptions in the literature. On microscopical examination of the sections (Fig. 8) the naked eye diagnosis was confirmed.

CASE 2.—(Surgical Nos. 46620 and 48293.) A white woman, aged 37, was admitted to The Johns Hopkins Hospital April 30, 1919, complaining of a lump in the left side of her neck. It had been present for four years and had grown gradually in size. When first observed it was very small, and her attention was directed to it by a stinging pain inside the throat. This occasional pain with sometimes a throbbing in the swelling was the only discomfort caused by the tumor. On her first admission to this hospital, October 5, 1918, a diagnosis of lympho-sarcoma was made and she was referred to Dr. Curtis F. Burnam for radium treatment. Numerous treatments failed to have any appreciable effect on the tumor. February 3, 1919, Dr. S. J. Crowe removed a small neighboring lymph gland for diagnosis. The pathological report was a round-cell sarcoma. Other treatments with radium were given but the swelling remained the same size.

The tumor extended from the lobe of the ear and the mastoid process to the middle of the sterno-mastoid muscle and anteriorly to a point midway between the angle and the symphysis of the mandible. The scar caused by the excision of the gland for diagnosis had not become attached to the tumor. The skin over the tumor was freely movable. The mastoid muscle was made taut by the tumor pushing it directly outward. There was a slight tendency to nodular formation in the anterior part of the growth. Upward it seemed to blend with the parotid gland. The tumor was doughy and gave almost the sensation of pitting on pressure. The trachea was in the midline. The tumor was slightly movable laterally but not vertically. It did not move on swallowing. Slight palpation of it provoked paroxysms of coughing.

The common carotid artery was displaced by the growth so that its bifurcation could be seen and felt on the antero-lateral aspect



Fig. 1.—Case 1, March, 1913. Before first operation.  
Sternomastoid muscle compressing the external growth,  
so that it is causing a conspicuous bulging of the pharyn-  
geal wall.



Fig. 2.—Case 1, as it appeared in 1919. Duration of  
tumor 11 years. Six years previously, the carotid artery  
was ligated and the sternomastoid muscle cut, thus effect-  
ing a decompression which permitted a lateral distortion  
of the growth. Note the pigmentation of the face and  
neck, and the prominence of the temporal blood vessels.  
There was no bulging of the pharyngeal wall.

Fig. 3.—Case 1. Side view, 1919. Note the large  
blood vessels.



Fig. 4.—Case 1. Posterior view, 1919.



Fig. 5.—Case 1. Two weeks after the operation.

Although a portion of the vagus nerve was removed, the  
vocal was not changed following the operation.

Fig. 6.—Case 2, Age 37. Duration of tumor 4 years.  
Skin yellow. Note the tense sternomastoid muscle.  
Carotid artery very superficial. There was marked bulg-  
ing of the right pharyngeal wall.



FIG. 9.—Specimen from Case 2. Weight .57 grams. Shows the infiltration of the common carotid artery. A, groove for external carotid artery.

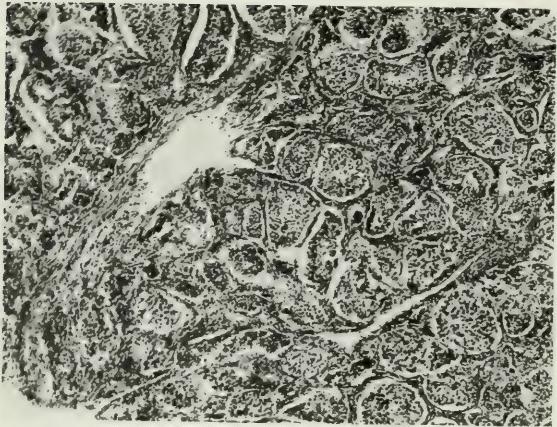


FIG. 10.—Photomicrograph from the specimen of Case 1. Very vascular. Note the cellular arrangement and hyperplasia in periphery. The nests of cells resemble the "cell balls" of the normal carotid body.

FIG. 7.—Specimen from Case 1. Weight 1.00 grams. The blood vessels are very prominent.



FIG. 11.—Case 3 Specimen. Yellowish white center, reddish black porphyry.



FIG. 10.—Case 2. Photomicrograph. The cellular arrangement is regular. There is infiltration all through, on soluble point cell infiltration. This tumor recurred, however, treatment over a period of several months.



FIG. 12.—Case 3. Photomicrograph. Very active hyperplasia; cells proliferating and invading into blood spaces. The blood spaces are filled with red blood cells.

Fig. 9.—Specimen from Case 2. Weight .57 grams. Shows the infiltration of the common carotid artery. A, groove for external carotid artery; B, groove for internal carotid artery.

of the growth, and its branches were easily palpable. The temporal pulse was equal on both sides. There was no disturbance of the circulation or nerve supply to the right side of the face. The pupils were equal and reacted normally.

The tumor had obliterated the right fauces and had pushed the pharyngeal wall across the midline of the throat and the soft palate forward. The mucous membrane was intact and was not attached to the growth. From the outer surface of the tumor to the swelling on the inner side of the neck the distance was 8 cm. There was slight atrophy of the right side of the tongue and it deviated a little to the right when protruded.

There was complete paralysis of the right vocal cord.

May 3, 1919. At the operation I was able to free the tumor anteriorly and from the mucous membrane of the throat. It was necessary to remove the sterno-mastoid muscle which seemed to be attached to the tumor. The carotid artery, jugular vein and vagus nerve were so inextricably bound up in the tumor that I could not free them. After dividing these vessels and the nerve below it, the operation was completed rapidly, although I had a little difficulty in securing the vessels at the base of the skull where they emerged from the tumor substance. It was necessary to cut the hypoglossal nerve and to remove part of the digastric muscle.

When the vessels and vagus nerve were divided the patient had some alarming symptoms. The pulse became slow; respirations ceased for a few moments and then became markedly Cheyne-Stokes in character. The right side of the face to exactly the midline of the forehead, nose and lips became absolutely blanched, while the left was pink. The right pupil was dilated. Recovery was gradual, the periods of apnea and the blanching of the face persisting for almost an hour.

The convalescence was complicated by the development of measles on the 10th day, and also by the discharge of some fluid from the wound. The character of this fluid was a light yellow serum so that the dressings were stained a golden yellow. As no tumor was left behind it was difficult for me to explain the yellow fluid. There was a mild infection, and the tissues about the wound reacted by exuding a yellow fluid almost like bile. This drainage persisted for four weeks.

The patient's voice was not affected, for she had already accommodated for a paralysis of the right cord before operation. The right pupil remained a little small. For a time there was some coughing and difficulty in swallowing due evidently to the paralysis of the hypoglossal and vagus nerves. The tongue deviated to the right on protrusion.

The tumor was pigmented, being a brownish color at the periphery and yellowish in the center. It was somewhat spongy and elastic. Weight, 57 gm. (Fig. 9). Measurements 7 x 5 cm. In the microscopical sections (Figs. 8 and 10), the tumor cells showed an alveolar arrangement. The connective-tissue septa were infiltrated with round cells and in some areas, with polymorphonuclear cells. This reaction may have been caused by the radium. There were numerous large blood vessels.

November 5, 1919. The patient returned on this date for observation. I was immediately struck by the appearance of her skin which was white and normal (she volunteered the information that she and her friends had noticed the improvement in her color), whereas at the time of operation it was dark and yellowish. There was no recurrence, and her only discomfort was an occasional coughing spell when eating. The right pupil was two-thirds the size of the left and reacted normally. In the throat the tonsillar space on the right side was deep, but otherwise appeared normal. No pulse could be felt in the right temporal artery. There had been no cerebral disturbance.

CASE 3.—(Surgical No. 33032.) A white man, 47 years old, was admitted to The Johns Hopkins Hospital October 13, 1913, complaining of a mass in the right side of his neck. His family and

past histories were unimportant in so far as they related to his trouble.

For 35 years there had been a swelling in the right side of his neck. Until two years before consulting Dr. Halsted it had remained about the size of a cherry. Then it had increased gradually for a year and a half, whereas for the last six months its growth had been more rapid. Six weeks before our observations began, the growth was explored by his local doctor who found the tumor so vascular that he did not think it safe to attempt its removal. After that the patient's voice had become hoarse and the speech more difficult.

There was a tumor in the upper right side of the neck descending to within 4 cm. of the clavicle. It was under the sterno-mastoid muscle and extended more into the anterior triangle of the neck than behind the muscles. The mass was roughly oval, measuring 10 cm. vertically and 8 cm. transversely. The skin was normal and freely movable except that the scar of the previous operation was attached to the tumor which appeared to be slightly nodular and very firm. Over its outer and anterior surface ran the carotid artery whose pulsations were easily seen and felt. There was no expansile pulsation of the swelling. Neither could a thrill nor bruit be detected in it.

There was ptosis of the right upper eyelid and a constriction of the right pupil. The patient insisted that these conditions had been present since childhood, and that they had no connection with the development of the tumor.

There was complete paralysis of the right vocal cord.

The operation was difficult and rather tedious on account of the numerous bleeding points. The vagus nerve was so caught in the growth that it had to be divided early in the operation. An opening was accidentally made in the internal jugular vein and there was a definite suction of air before the vessel was clamped and ligated. The artery which ran over the anterior part of the tumor was freed and thrown mesially. At about this stage in the operation the patient became somewhat cyanotic and developed a rapid pulse. The tumor which extended well up to the base of the skull, but which by this time was well freed, was quickly removed. The patient's condition did not, however, improve and death came at about the time the wound was closed. The operator felt that death was connected with the stimulation of the vagus nerve and possibly, also, with the suction of the air into the jugular vein. There was very little loss of blood.

The specimen was a slightly lobulated mass measuring 7 x 4 x 3.5 cm. It was a dark blood color. On section the center of the tumor was rather white and fibrous and sent radiating strands of this tissue into the dark red, cellular periphery (Fig. 11). The tumor was rather spongy and on pressure a frothy bloody fluid came from the cut surface. The histological structure was so typical of the tumors that are often called perithelial angi-sarcomas (Fig. 12) that, at that time, a diagnosis of a perithelial or endothelial angi-sarcoma of the neck was made. That the tumor was associated with the carotid body did not then occur to us. As we now look back on the case everything about it is typical, both clinically and pathologically, of carotid body tumors. The color, the structure, the position in the neck and its relation to the nerves and blood vessels of the neck leave no doubt that the growth originated in the carotid body.

#### DISCUSSION

The discussion of a condition so well described in the literature is scarcely justifiable unless something new can be said. There is probably not yet any unanimity of opinion as to the origin of the carotid gland. It seems to be a question as to whether it comes from the endoderm, mesoderm, or ectoderm. Much has been written about this subject. Kohn believes that the sympathetic ganglia and carotid body arise from

the same type of cells. Such an origin is the most generally accepted view. There seems to be no doubt that it belongs to the chromaffine system and its relation to the sympathetic nervous system seems to be very like that which exists between the medulla of the suprarenal body and the sympathetic nerves.

1. *Pathology*.—Various authors have regarded "carotid body tumors" as peritheliomas, endotheliomas, adenomas, epitheliomas, perithelial angio-sarcomas, etc. Slight variations in the histological structure have no doubt led to these differences of nomenclature. However, the behavior of all of these tumors and the similarity in general of their gross and histological appearance, would seem to indicate that "tumor of the carotid body" has been regarded as a nomenclature of sufficient pathological specificity. The description of their behavior in life, their gross appearance and the general similarity of the histological pictures leave no doubt that under the appellation of "carotid body tumor" a certain pathological condition of the carotid body has been well described. The tumors reported in this paper correspond to the accepted description of "carotid body tumors." Many conditions described as carotid body tumors have been discarded by various authors because they did not correspond to this particular description. "Potato tumors," as described by Hutchinson and Gilford, do not come within the scope of the accepted meaning of "carotid body tumors." Certainly, the tumor described by Wooley and Fee appears to have been an aberrant thyroid.

(a) *Hyperplasia*.—But, must we not ask ourselves if the carotid body may not be the seat of various pathological conditions? May not the carotid body, like the thyroid, be subject to changes similar to those that occur in the thyroid or any other gland? One would not speak of exophthalmic goitre or a local hyperplasia of the thyroid gland as a "thyroid gland tumor." It seems to me that we are doing this thing, however, in speaking of "carotid body tumors." The histology of so-called "carotid body tumors" appears to bear the same relation to the structure of the normal carotid gland as the histology of exophthalmic goitre bears to the normal structure of the thyroid gland. In the case of carotid body tumors differences of structures have no doubt given rise to the differences of opinion as to the best name for these tumors, as perithelioma, endothelioma, angio-sarcoma, alveolar sarcoma, adenoma, perithelial angio-sarcoma, etc. Differences in the amount of stroma, and parenchyma of cases of exophthalmic goitre do not lead any more to a confusion of terms—we speak of hyperplasia of the thyroid gland. I believe that it would simplify matters to regard the now accepted carotid body tumors as a local or general *hyperplasia* of the carotid gland, the variations in the amount of stroma and parenchyma accounting for the slight differences in the photomicrographs that appear in the literature.

(b) *Adenomata*.—It may be said that a hyperplastic condition would most likely involve both carotid bodies. Only a few such cases have been recorded. It would obviously be very difficult to determine whether any condition arising in

a structure so small as the carotid body began in part or all of it. If "carotid body tumors" are due to a hyperplasia of a part of the gland, adenomata would be a more appropriate term to use. The unilateral "carotid body tumors" that have been described may have been local hyperplasias—adenomata—while the bilateral cases may have been true hyperplasias of the entire substance of both glands.

(c) *Malignant Tumors*.—Although it seems clear that most authors have tried to limit the name "carotid body tumor" to a specific local or general hyperplastic condition of the gland, it is certain that malignant changes in a benign hyperplasia, or true primary malignant tumors have been observed. Da Costa says that carotid body tumors may become malignant. And why should not in some cases a hyperplasia or adenoma of the carotid body become malignant? Similar changes are seen in the thyroid, and perhaps, occur in the adrenals or in the hypophysis. If one admits that the "potato tumors" described by Hutchinson and Gilford developed in the carotid body, then it seems certain that we have described for us primary malignant conditions of the carotid body. Gilford describes two cases that were apparently sarcomas, while his third case seems to have been a carcinoma. They were rapidly fatal, non-pigmented cellular tumors whose structures varied markedly from that of the carotid body hyperplasia. So hyperplasia, hyperplasia with malignant change, sarcoma and carcinoma of the carotid body have all been reported. Confusion has been caused by trying to limit the term "carotid body tumor" to mean the pigmented slow-growing tumor which appears to be certainly a hyperplasia or adenoma of the normal carotid body. Other conditions, such as cysts or myxomas, may have been seen by surgeons but not recognized as arising from the carotid gland.

Without going further into the pathology of adenomata of the carotid gland which are very definite lesions and which have been so admirably described by many authors as "carotid body tumors," my remarks will be confined to the discussion of some observations which may have a bearing upon the diagnosis, the treatment, and possibly the function of the carotid gland.

2. *Diagnosis*.—Keen, who was the first American to write at length about these tumors, has given us the very best illustrations and descriptions of their pathology. He speaks of twelve points which may be helpful in the making of a proper diagnosis: (1) The position at the bifurcation of the carotid artery, (2) movability laterally but not vertically, (3) ovoid in shape, (4) smooth and not lobulated, (5) single, (6) transmitted pulsation, (7) bruit and thrill, (8) bulging of the wall of the pharynx, (9) pupils occasionally constricted, (10) slow growth, (11) long duration, and (12) a rather firm elastic consistency. Speaking negatively he says they are: (1) Not tender, (2) not painful and (3) the deformity is the main complaint. Funke and others call attention to numerous very similar characteristics that ought to help in the making of a correct diagnosis.

Yet the fact remains that it is very unusual for these tumors to be diagnosed correctly before operation. Reclus

and Chevassu, Kopfstein and Maydl, Da Costa, Kocher (in the case reported by Licini), Boni, Lilienthal, and Winslow have correctly made a diagnosis of carotid body tumor before operation. Most of these authors, however, have profited by mistakes in their first cases and thus have diagnosed correctly those that they met with subsequently. An important point upon which Kocher based his diagnosis of the case reported by Licini was the fact that the carotid artery seemed to run through the tumor. Funke says that the large vessels of the neck may be caught by these growths and pushed laterally.

(a) *Position of the Artery.*—Thus, what ought to be a great help in the differential diagnosis of these tumors, is touched upon very lightly in the literature. I know of no other growth of the neck which catches, fixes and carries the carotid artery with it. Enlargement of the lymphatic glands usually leaves the artery in its course or perhaps rolls it a little anteriorly or posteriorly. Large benign thyroid conditions always throw the carotid artery posteriorly, so that in large colloid goitres it may be felt as a freely movable vessel and not far from the midline of the neck. Malignant thyroid tumors may invade, but do not distort, the course of the common carotid artery. So, branchial cleft cysts, hygromas and other benign tumors of the neck may roll the artery so that it becomes a slightly displaced, freely movable vessel.

Gomez gives illustrations of the various positions of the carotid gland. The commonest position is on the mesial side of the bifurcation of the common carotid artery. Even the six variations are on the mesial and posterior side of the artery, and within its sheath, so that any enlargement would catch this vessel. In most of the illustrations of carotid body tumor (see Keen and Steindl) the tumor is lodged in the bifurcation of the artery like a nest in the fork of a tree. The groove caused by the internal and external carotid arteries are, as in our cases, on the lateral or antero-lateral aspect of the tumor. Often only a little of the tumor is represented as projecting between the forks of the vessel. In large carotid body tumors the sterno-mastoid muscle is pushed laterally so that from the tumor to the clavicle it may stand out as a rather tense cord; and the common carotid artery or its branches may be seen and felt very superficially, running over the surface of the tumor, but cannot be displaced (Fig. 6).

(b) *Effect on the Vagus Nerve and Pharynx.*—When carotid body tumors attain a moderate size it is usual for them to cause a bulging of the pharyngeal wall, which may even be pushed to or beyond the uvula. Some observations on Case 1 of this report lead us to believe that it is the restraining influence of the carotid artery and sterno-mastoid muscle that tends to make the tumor grow mesially. Paralysis of the recurrent laryngeal nerve has been noted frequently and was present in all three of our cases. This fact together with the relatively infrequent occurrence of disturbances of speech following operations would lead me to believe that the carotid body tumors of considerable size do usually cause a paralysis of the vocal cord. It is interesting that in two of our cases the patients gave no history of ever having disturbance

of speech, and yet the routine examination of the throat showed that both of them had a paralysis of the vocal cord on the side of the tumor. Apparently, a very gradual paralysis of the recurrent laryngeal nerve may not affect the voice very noticeably. Perhaps in a couple of cases the hypoglossal nerve has been paralyzed by these tumors.

(c) *Aneurysms.*—Numerous cases of very vascular adenoma of the carotid body, as in Case 1, have been diagnosed as carotid aneurysms. A thrill and bruit, and a definite expansile pulsation may be very misleading. There is no doubt that the pulsation of these tumors may be definitely expansile. This was true in Case 1, both before and after ligation of the common carotid artery. Malignant or pulsating exophthalmic goitres have been mistaken for aneurysms. The mistake would be more common if the thyroid gland were situated at the bifurcation of the common carotid artery.

3. *Function.*—Nothing is known about the function of the normal carotid body, nor have any functional disturbances been described in connection with its hyperplasia. In the two cases upon which I operated, the pigmentation of the body has been a striking clinical observation. Case 1 showed an erythematous flush over the neck, a suffusion of the face and a yellowish dark color of the entire body. Case 2 showed a light lemon yellow color of the entire body. The pigmentation in both of these cases cleared up completely after the removal of the tumors. In both cases the adenomata were completely removed. The wound of Case 2, however, became slightly infected and drained a light bile-colored fluid for almost four weeks. Were the body juices saturated with a chromaffine substance? These patients were the opposites of exophthalmic goitre patients—their actions were slow, their speech deliberate; they were not nervous and there was no tachycardia. The pigmentation was certainly associated with the hyperplasia of the gland. The slow actions and slow queer speech may always have been characteristic of my patients and not due to the growth.

4. *Treatment.*—Surgeons cannot be proud of the results of the surgical treatment of carotid body tumors. A mortality of between 27 and 30 per cent, and a morbidity nearly as high, should make one hesitate before operating on these conditions. Most of these patients have been operated upon for cosmetic reasons and probably would not have submitted to an operation had they known that in the vast majority of cases it was necessary to divide the carotid artery, the jugular vein, the vagus and hypoglossal nerves. Pneumonia, hemorrhage, cerebral anemia, and infection are given, in the order of their importance, as the causes of death. Pneumonia is thought to be favored by section of the vagus nerve and, if this be so, will probably remain the greatest cause of death following operations upon tumors of the carotid gland. In the present age surgeons pay so much attention to hemostasis that deaths from hemorrhage would not be likely to occur. Dr. Halsted has suggested that deaths and paralyses due to cerebral anemia may be lessened or prevented by producing a gradual occlusion of the artery by a metal band before extirpating the

tumor, a procedure which would insure to the brain a better collateral circulation when the major operation is done.

The advisability of surgical treatment of tumors of the carotid body has been questioned by eminent surgeons. Keen, Da Costa, Reclus and Chevassu advise against operation, when the tumor is large and it is almost certain that its removal will necessitate sacrificing the carotid artery, jugular vein and vagus nerve. Small tumors that can be freed from these important structures should be removed. Preliminary partial or complete ligation of the common carotid artery will lessen the danger of cerebral disturbances that may follow the extirpation of large tumors. Yet after a preliminary ligation of the artery the control of hemorrhage may be very difficult. In the first case reported in this paper the tumor, which is the largest on record, was successfully removed six years after the ligation of the common carotid artery, but the control of hemorrhage was one of the most difficult surgical problems I have met with. That an adenoma or hyperplasia of the carotid body should be removed in order to avoid the danger of its becoming malignant is not well proven. The very long duration (1 to 40 years) of the growths in the cases reported, would seem to indicate that a carotid adenoma is not particularly prone to become malignant. For truly malignant tumors of the carotid gland, very radical operations should be performed. In the one, or possibly two cases, of an enlarged carotid body in which malignancy has ensued, the changes in the character of the tumor have been very like those observed when a carcinoma develops in an adenomatous or colloid goitre.

(a) *Decompressive Operation.*—Experience with Case 1 leads me to suggest what might be called a decompressive operation. After a division of the sterno-mastoid muscle and the simple ligation of the common carotid artery the tumor which had previously projected across the midline of the pharynx came out laterally and posteriorly, so that six years later the pharynx appeared normal. When, therefore, a surgeon does not feel that he can or ought to remove a hyperplastic carotid body it may be feasible to cut the sterno-mastoid muscle, and possibly to ligate the common carotid artery, in order to relieve an encroachment upon the pharynx, and to facilitate the removal of the growth at a later date by allowing it to become more superficial.

#### SUMMARY

1. The slow growing pigmented tumor of the carotid gland, heretofore described as "carotid body tumor" is a simple hyperplasia of a part or all of the normal gland; it should be designated as an adenoma or hyperplasia of the carotid body. In rare instances a malignant condition may develop in it.

2. A "potato tumor of the neck" may be a primary sarcoma or carcinoma of the carotid body.

3. The relation of the common carotid artery to enlargements of the carotid gland ought to help us in arriving at a correct diagnosis. This artery is caught and carried laterally or anteriorly so that it and its branches may often be readily felt on the surface of the tumor.

4. A bulging of the pharyngeal wall and a paralysis of a vocal cord are frequently observed in an enlargement of the carotid body. The paralysis may be detected only by direct examination of the cords, inasmuch as disturbances of speech do not usually occur.

5. Yellowish pigmentation of the body, flushing of the head and neck and a slow, somewhat apathetic state of mind may result from hyperplasia of the carotid gland.

6. The mortality of operations for hyperplasia of the carotid body has been very high. Preliminary ligation, partial or complete, of the carotid artery, and careful hemostasis at the second operation may reduce it materially.

7. In some cases in which an operation is imperative on account of the size of the growth it may be wiser to do a decompressive operation than to attempt extirpation of the tumor. Then, after the tumor dislocates laterally and becomes more superficial, its removal will be easier and safer, particularly if the artery has been tied at the time of decompression.

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# A STUDY OF THE HÆMODYNAMIC REACTIONS OF THE CEREBROSPINAL FLUID AND HYPOPHYSEAL EXTRACTS

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## SYNOPSIS

### 1. Introduction.

Review of literature.

Presupposition of hæmodynamic substance in cerebrospinal fluid.

### 2. General plan of and methods employed in this and in previous researches.

### 3. Protocols with experimental data.

### 4. Comparison of hæmodynamic, glycogenic and diuretic effects of cerebrospinal fluid and hypophyseal extracts.

### 5. Summary and inference.

### 6. Nature of depressor substance.

a. Relation to choline.

b. Effect of stimulation of hypophysis on blood pressure.

c. Effect of stimulation of superior cervical ganglion.

d. Similarity to histamine.

### 7. Conclusion.

Although the existence of the pituitary gland had been vaguely known for several centuries, it remained for Marie in 1888-1889 to give impetus to the closer study of the gland by associating certain anomalies of skeletal growth with tumor or hypertrophies of that structure. In 1895 Schaefer and Oliver<sup>1</sup> showed that its infundibular lobe possessed a blood pressure raising substance, and since that time a mass of literature has appeared concerning the structure and physiology of the gland as one of the endocrine series. Most conflicting statements of its power as a hæmodynamic, glycogenic, diuretic, galactagogic and peristaltic agent have been made and have added confusion to our meager knowledge of the intercorrelated action of the ductless glands. Granting that it has a specific internal secretion, the method and manner of its production and disposition, its chemical composition, its characteristic properties, its relation to the body economy in health and disease are still fruitful problems for future investigation.

Herring,<sup>2</sup> in 1908, advanced the theory that the secretory activity of the posterior lobe of the hypophysis, represented principally by faintly staining hyaline bodies, passes by way of the infundibular stalk and finds its way between the ependymal cells into the cavity of the third ventricle where it enters into solution with the cerebrospinal fluid and finds its way into the blood stream of the dural sinuses.

Cushing and Goetsch,<sup>3</sup> in 1910, confirmed these findings, basing their evidence (1) on the histological picture of the increase of and migration of these hyaline bodies towards the ventricle when the gland is subjected to various operative procedures and (2) on the supposed presence of a hæmodynamic substance in the cerebrospinal fluid giving reactions quite comparable to those due to posterior lobe secretion.

These conclusions were subsequently questioned by Edinger,<sup>4</sup> (1911) who by histological studies and by injection methods was led to believe that the hyaline bodies pass along the stalk to a certain zone where the infundibular process joins the tuber cinereum and the interneuroglial pathways abruptly cease, and that the hyaline bodies do not enter the ventricle.

Crowe and Evans (unpublished communication) by intravital staining, moreover, have shown that the posterior lobe stains deeply up to a certain and perhaps similar zone beyond which the tuber cinereum and brain remain unstained.

Lewis, Miller and Matthews<sup>5</sup> (1911) were unable to demonstrate the presence of a pressor substance in the infundibular stalk, a part of the gland in which the hyaline bodies are presumably present; this finding is opposed to Herring's views unless the bovine gland has an anatomical arrangement different from the canine.

The observations of Cushing and Goetsch (1911) seem to show that concentrated cerebrospinal fluid from various clinical cases, when injected intravenously into rabbits and dogs, produced hæmodynamic reactions with increased amplitude of the pulse, similar to those from posterior lobe extract injections. Moreover, diuresis was almost invariably evoked; peristalsis was often stimulated with resultant catharsis; the smooth muscle of the uterus and bladder was brought into contractile states, and glycogenic effects were produced with resultant glycosuria. Subsequently Carlson and Martin<sup>6</sup> (1911), using somewhat different methods, concluded that cerebrospinal fluid, from dogs at least, had no pressor or depressor effect upon the canine circulation, and that the intravenous injection of whole gland, anterior or posterior lobe of the pituitary body, does not produce sugar in the urine. These are definitely contradictory findings and form the subject with which this paper is mainly concerned.

The observations of Cushing and Goetsch were based primarily upon the reaction obtained by the intravenous injection of concentrated solutions of cerebrospinal fluid of human origin. They usually employed 2 c. c. of a 30-1 or a 20-1 concentration and contrasted the results with the reactions furnished by small amounts of whole gland or individual lobe hypophyseal extracts. It is well to note that in this procedure there was employed a large amount of stimulating substance per unit volume of fluid injected. The observations of Carlson and Martin, on the other hand, were based upon the intravenous introduction of a large amount of unconcentrated canine cerebrospinal fluid into an animal of the same species, the body fluid volume being kept constant by a pre-

liminary bleeding of the animal in amount equal to the fluid injected. Under these circumstances there was utilized a small amount of stimulating substance per unit volume of fluid injected. To determine the glycogenic effect they introduced intravenously an extract made from 1-10 whole canine glands into another dog without producing glycosuria.

It is quite obvious that the conflicting observations in the above researches are due to the different methods employed and pertain to the degree of concentration of the injected fluid. Undoubtedly the concentration of cerebro-spinal fluid of human or bovine origin in a proportion of 30-1 or 20-1 produces a strongly hypertonic, well-nigh saturated solution, and Carlson has rightly raised the question regarding the interpretation of haemodynamic reactions caused by the introduction even of small amounts of such concentrated solutions into small animals. In acceptance of this criticism it was thought advisable in this investigation to make an "artificial spinal fluid" free from organic substances and use this as a control for the concentrated spinal fluid.

Briefly stated the object of this present investigation is a study of the physiological effects of intravenous injections of unconcentrated and concentrated spinal fluid, human, bovine and artificial, in contrast with similar injections of hypophyseal extracts, anterior lobe, posterior lobe, pars intermedia and whole gland, in the hope of reaching some definite conclusion regarding the presence or absence of the pituitary secretion in the cerebrospinal fluid.

#### PREPARATION OF FLUIDS

*Human Spinal Fluids.*—These were obtained during operation or clinical examination from 39 separate cases by ventricular or lumbar puncture. Most of these specimens, as seen from the appended list, were from patients suffering from conditions with obstruction to the cerebrospinal outflow and yielded on various occasions spinal fluid in considerable amounts. Carlson has intimated that these were pathological fluids but in the absence of any specific infective process one scarcely knows what constitutes a pathological cerebrospinal fluid. It is improbable that any long-standing obstruction would produce any marked chemical or organic change in the fluid. The fluid of internal hydrocephalus, for example, is generally considered to be normal cerebrospinal fluid. The fluid used in these experiments was collected in sterile bottles and, if not used immediately, sterilized at low heat and kept in a dark place. On prolonged standing it sometimes became slightly opalescent due no doubt to hydrolytic cleavage of some of the organic material. When used in concentrated form it was evaporated either on the water-bath or under reduced pressure *in vacuo*; the two different methods of concentration evidently had no appreciable effect upon the resultant concentrate as far as the subsequent physiological reaction was concerned. The sources of the fluid are given in Table 1.

TABLE 1  
HUMAN SPINAL FLUID

Fluid No.	Diagnosis	No. fluids	Amount c. c.	Source of fluid
1 R-k ...	Cerebellar tumor.....	9	765	Ventricular.
2 A-n ...	Epilepsy .....	2	150	Ventricular.
3 S-r....	Cerebellar tumor.....	1	60	Ventricular.
4 S-z....	Cerebellar tumor.....	1	50	Ventricular.
5 G-z ...	Epilepsy.....	2	70	Lumbar and ventric.
6 K-t ...	Infundibular tumor .....	1	60	Ventricular.
7 C-d ...	Internal hydrocephalus .....	2	50	Lumbar.
8 G-s ...	Hypopituitarism .....	1	60	Lumbar.
9 W-l ...	Hypopituitarism .....	1	25	Lumbar.
10 F-y ...	Cerebral tumor.....	1	50	Lumbar.
11 C-s... .	Cerebellar tumor-hydrocephalus..	2	120	Lumbar and ventric.
12 S-y ...	Temporal lobe tumor.....	8	410	Lumbar and ventric.
13 B-r ...	Temporal lobe tumor.....	6	460	Lumbar and ventric.
14 Be-r ...	Cerebellar tumor.....	4	120	Lumbar and ventric.
15 S-y....	Pituitary tumor.....	1	50	Lumbar.
16 S-h ...	Cerebellar tumor.....	2	300	Ventricular.
17 D-r ...	Hydrocephalus .....	4	200	Ventricular.
18 K-z ...	Hypopituitarism.....	1	30	Lumbar.
19 S-w ...	Pituitary tumor.....	1	30	Lumbar.
20 T-t....	Cerebellar tumor.....	1	50	Ventricular.
21 H-m ..	Pontine tumor .....	1	100	Ventricular.
22 N-s ...	Hydrocephalus .....	4	240	Ventricular.
23 K-z ...	Hydrocephalus. Pineal tumor...	2	100	Lumbar and ventric.
24 M-k ...	Hydrocephalus .....	8	450	Ventricular.
25 T-w ...	Hydrocephalus. Pineal tumor?..	4	120	Ventricular.
26 G-n ...	Cerebellar tumor.....	6	240	Ventricular.
27 G-n-n ...	Cerebellar tumor.....	1	40	Ventricular.
28 P-n-s ...	Cerebral tumor .....	4	160	Ventricular.
29 C-y ...	Cerebellar tumor.....	1	40	Ventricular.

*Bovine Spinal Fluid.*—Large amounts of sterilized bovine cerebrospinal fluid were obtained through the courtesy of Armour & Co. and of Parke Davis & Co. The fluid from the former was slightly dark brown in color and had a small flocculent precipitate; that from the latter was clearer and lighter in color. Both were sterile on culture. One portion of each fluid was evaporated down to the required concentration and the other portion evaporated to dryness, the residue finely pulverized and weighed amounts of the powder, in aqueous solutions, used for subsequent injections.

*Artificial Spinal Fluid.*—These were solutions containing the inorganic salts found in normal cerebrospinal fluid. They were made according to the formula given by Halliburton<sup>1</sup> (Sp. fluid A) and Meztrezat<sup>2a</sup> (Sp. fluid B).

FLUID A	FLUID B
Water .....1000.	Water .....1000.
NaCl ..... 7.098	NaCl ..... 8.362
KCl ..... 0.33	KCl ..... 0.397
CaCl <sub>2</sub> ..... 0.186	

The NaCl to KCl ratio was 21 to 1 in both solutions. At times there was added the normal dextrose content of 0.07 per cent. These solutions were practically Locke's solutions.

*Pituitary Preparations.*—Commercial pituitary extracts were obtained likewise from Armour & Co., Parke Davis & Co., or were bought in the open market. Inasmuch as such preparations were found to differ markedly in their effect, care was taken to use the same preparation on the same animal in order to get comparative results. Absolutely fresh bovine extracts were made from glands secured from the local abattoir and several hundred glands were sent to the laboratory packed in ice by Armour & Co. From these glands all capsular and adventitious matter was carefully removed and the tissues were carefully separated preliminary to making extracts of (1) whole gland, (2) anterior, (3) posterior lobe, (4) pars intermedia and (5) the colloid material found in the interlobular cleft. These different portions of tissue were then separately ground with sand and with a small amount of physiological salt solution. The extracts in each case were separated out by passing through a Buchner press and evaporated to dryness either by pan evaporation or under reduced pressure *in vacuo*. The dried preparations were then finely pulverized and weighed amounts were separately used for injections. In this manner 625 glands furnished 60.2 gms. of anterior lobe, 16.2 gms. of posterior lobe and 3 gms. of pars intermedia, while 100 glands furnished 14.8 gms. of whole gland extract. On several occasions fluid extracts were made from fresh material and used immediately for injection purposes.

*Animals.*—The animals used were mainly rabbits and dogs. It was found unnecessary to anaesthetize the former for the observations, but ether and occasionally chloretone was employed for the dogs. Pulse tracings were taken from the carotid and the injections were made into the jugular and occasionally into the saphenous vein. Urine flow was counted in drops from a small glass catheter passed into the bladder through the urethra. In order to have sufficient free available glycogen and plenty of body fluid for diuretic effects, care was taken to have the animal well fed with carbohydrate and with plenty of fluid before the experiment. Injections consisted of 2 or 3 c. c. in volume. This amount was found to have no appreciable effect upon the blood pressure.

Results of the injections are given in the protocols on pages 188-191.

As can be seen from the abbreviated protocols, the resultant reaction obtained from the injection of cerebrospinal fluid, artificial spinal fluid, anterior, posterior lobe, pars intermedia and whole gland of the hypophysis are extremely variable, depending not only upon the species of animal used but also upon the individual animal itself. All reactions fall quite readily in the above groupings, considering any change below 10 mm. of mercury, a low limit, as negligible or negative. The results of injection of pituitary extract, definite as such reactions are supposed to be, are in fact so variable that one is led to doubt somewhat the existence of a specific secretion. It is also claimed that successive injections render the animals insensitive to the reaction, and as a consequence, single injections have been used in several researches. That this is probably an overstatement is readily seen from results in this com-

parative study in which as many as 8 or 10 injections have been given in the same animal with a gradual change in the reaction. It is quite evident that an erroneous impression can be obtained from a single chart or injection, and this no doubt accounts for the marked confusion upon the subject in the literature. Definite conclusions can only be obtained by the comparative study of a series of injections in the same and in many animals.

#### DISCUSSION OF RESULTS OF INJECTIONS

**1. Cerebrospinal Fluid Injections.**—Moderate concentrations of human and bovine spinal fluid when injected intravenously usually cause a slight depressor effect followed by a more or less prolonged pressor effect. With increase in concentration these effects are more pronounced. These reactions are usually of a transient character but on marked concentration the effect may be prolonged. Record 1\* shows clearly the augmentation of depressor and pressor effect with increase in concentration of fluid, while Record 2 shows a typical response from a 20-1 concentration of human spinal fluid. This is very similar to the effect described by Cushing and Goetsch in their original article and considered by them as indicative of the presence of a posterior lobe secretion.

**2. Artificial Spinal Fluid Injections.**—Intravenous injections of this fluid in concentrated form give also usually a depressor response quite similar to that from similar concentrations of human and bovine spinal fluid. Records 3, 3-a and 4 give quite typical responses to injections of artificial spinal fluid contrasted with human spinal fluid. Records 5 and 6 show a similar contrast between artificial fluid and bovine spinal fluid.

**3. Hypophyseal Injections.**—The responses to injections of hypophyseal extract are very variable both when used as successive injections in the same animal or in different animals and we have a varied assortment of confusing reactions and blood pressure curves. The classical posterior lobe reaction is supposed to consist of a transient depressor effect followed by a long enduring pressor response persisting for some 10 minutes and frequently over 20 minutes. Such curves are shown by Records 7, 8 and 9, which reveal a moderately good response to posterior lobe injections in an animal which gives practically negligible responses to injections of concentrated artificial and human spinal fluid. Record 10 also shows another posterior lobe response in which the depressor effect is practically missing. That these glandular manifestations as far as the blood pressure raising effect is concerned may be extremely variable is readily seen by a series of injections and reactions in four dogs, R<sub>2</sub>, S<sub>2</sub>, T<sub>2</sub>, V<sub>2</sub>, essentially similar in all respects as far as weight and outward general condition are concerned. Records 11 to 22 show a series of three quantitatively similar injections into each animal of anterior, posterior and pars intermedia, extracts carefully made in the laboratory from the respective parts of the ox gland. The varied results obtained from identical injections into similar animals clearly demonstrate the difficulty of ascribing specific effects to differentiated

\* To economize space, the blood pressure curves are presented in outline, drawn and reduced from the kymograph tracing.

## PROTOCOLS

Date	Case	Injections			Blood pressure effects—mm. Hg.				Urine		Remarks	
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
3-3-11	Rabbit C.	1	2 c. c. (10-1)	.....	.....	.....	126-154	.....	.....	.....	.....	Vent. fluid—Roebuck.
		2	" (10-1)	.....	.....	.....	140-156	.....	.....	.....	+	No urine.
		3	.....	1/20 gm.	.....	.....	86-186	.....	.....	.....	.....	
		4	.....	.....	1/80 "	106-106	.....	.....	.....	.....	.....	
		5	2 c. c. (10-1)	.....	1/80 "	.....	102-120	.....	.....	.....	+	
3-7-11	Rabbit D.	1	" (1-1)	.....	.....	.....	.....	130-120-130	104-16-146	Slight.	—	Spinal fluid, ox.
		2	" (1-1)	.....	.....	.....	.....	124-119-136	"	—	"	" "
		3	" (2-1)	.....	.....	.....	.....	110-88-132	+	—	"	" "
		4	" (3-1)	.....	.....	.....	.....	108-94-135	.....	—	"	" "
3-9-11	Rabbit E.	1	" (1-1)	.....	.....	.....	112-122	.....	.....	Slight.	.....	" "
		2	" (2-1)	.....	.....	.....	116-122-126	.....	.....	—	—	" "
		3	" (4-1)	.....	.....	.....	116-96-126	.....	.....	—	—	" "
		4	" (6-1)	.....	.....	.....	128-110-138	.....	.....	—	—	" "
		5	" (10-1)	.....	.....	.....	108-94-135	.....	.....	—	—	" "
		6	.....	1/20 gm.	.....	100-120	.....	.....	—	+	—	
		7	.....	1/40	.....	.....	78-60-88	—	—	—	+	
3-10-11	Rabbit F.	1	2 c. c. (1-1)	.....	.....	100-108	.....	.....	.....	—	—	Lumbar fluid—Roebuck.
		2	" (2-1)	.....	.....	102-108	.....	.....	.....	—	—	" "
		3	" (4-1)	.....	.....	106-110	.....	.....	.....	—	—	" "
		4	" (6-1)	.....	.....	104-110	.....	.....	.....	—	—	" "
		5	" (10-1)	.....	.....	108-100-118	—	—	—	—	—	" "
		6	" (10-1)	.....	128-134	.....	.....	.....	.....	—	—	" "
		7	" (10-1)	.....	.....	128-110-128	—	—	—	—	—	Vent. "
		8	" (10-1)	.....	102-90-100	—	—	—	—	—	—	" "
		9	.....	1/80 gm.	.....	80-88	—	—	—	—	—	
		10	.....	1/40	.....	52-58-40	—	—	—	—	—	
		11	.....	1/20 "	32-42	.....	—	—	—	—	—	
3-16-11	Rabbit F'.	1	2 c. c. (10-1)	.....	.....	124-140	.....	.....	.....	—	—	Lumbar fluid—Roebuck.
		2	" (20-1)	.....	.....	.....	130-124-144	—	—	—	—	" "
		3	.....	1/80 gm. A.	.....	134-112-136	—	—	—	—	—	" "
		4	.....	1/20 "	.....	108-death.	—	—	—	—	—	
		5	2 c. c. (40-1)	.....	.....	.....	.....	.....	.....	—	—	
6-6-11	Rabbit G.	1	" (10-1)	.....	.....	.....	104 82-104	—	—	—	—	Vent. fluid—Smith.
		2	" (10-1)	.....	.....	.....	98-80-104	—	—	—	—	" "
		3	" (10-1)	.....	1/20 gm.	70-100	—	—	—	—	—	Spinal fluid, ox.
		4	.....	.....	.....	—	—	—	—	—	—	
6-7-11	Rabbit H.	1	2 c. c. (20-1)	.....	.....	.....	118-10-128	—	—	—	—	" "
		2	" (20-1)	.....	.....	.....	110-86-132	—	—	—	—	Vent. fluid—Smith.
		3	.....	1/20 gm.	.....	100-80-120	—	—	—	—	—	
6-8-11	Rabbit I.	1	2 c. c. (15-1)	.....	.....	.....	120-51-168	—	—	—	—	Spinal fluid, ox.
		2	" (15-1)	.....	.....	.....	110-74-118	—	—	—	—	Vent. fluid—Smith.
		3	.....	1/20 gm.	.....	100-120	—	—	—	—	—	
6-9-11	Rabbit J.	1	2 c. c. (15-1)	.....	.....	136-172	—	—	—	—	—	Spinal fluid—Dyer.
		2	" (20-1)	.....	.....	.....	130-116-152	—	—	—	—	" "
		3	" (20-1)	.....	.....	118-144	—	—	—	—	—	Vent. fluid—Smith.
		4	" (20-1)	.....	.....	.....	110-100-126	—	—	—	—	Spinal fluid—Stickley.
		5	(2 c. c. water)	.....	106-108	—	—	—	—	—	—	" " Cleland.
		6	2 c. c. (20-1)	.....	.....	106-120	—	—	—	—	—	
		7	.....	1/20 gm.	22-60	—	—	—	—	—	—	
		8	.....	1/10 "	78-90-death.	—	—	—	—	—	—	
6-10-11	Rabbit K.	1	2 c. c. (20-1)	.....	.....	102-death.	—	—	—	—	—	Dyer.
		2	" (20-1)	.....	.....	88-16-death.	—	—	—	—	—	" "
6-12-11	Rabbit L.	1	" (20-1)	.....	.....	.....	106-92-138	—	—	—	—	
		2	.....	.....	.....	.....	110-102-140	—	—	—	—	
		3	" (15-1)	.....	.....	.....	104-98-130	—	—	—	—	Katz.
6-14-11	Rabbit M.	1	" (20-1)	.....	.....	.....	106-92-138	—	—	—	—	Parturient rabbit.
		2	" (12-1)	.....	.....	.....	110-102-140	—	—	—	—	Spinal fluid—Wall.
		3	" (15-1)	.....	.....	.....	104-98-130	—	—	—	—	
		4	.....	.....	.....	—	—	—	—	—	—	
6-16-11	Rabbit N.	1	" (15-1)	.....	.....	.....	103-82-121	—	—	—	—	" " Dyer.
		2	" (15-1)	.....	.....	.....	103-95-137	—	—	—	—	" " Shaw.
		3	.....	1/20 gm.	.....	80-72-118	—	—	—	—	—	
		4	.....	.....	.....	—	—	—	—	—	—	
6-26-11	Rabbit O.	1	.....	2 c. c. (20-1) water.	.....	.....	84-66-98	—	—	—	—	
		2	.....	.....	82-74-82	—	—	—	—	—	—	
		3	2 c. c. (20-1)	.....	.....	.....	82-60-108	—	—	—	—	Vent. fluid—Taggart.
		4	.....	1/20 gm.	.....	—	—	—	—	—	—	
		5	.....	1/20	72-86	—	—	—	—	—	—	
6-27-11	Rabbit P.	1	3 c. c. (1-1)	.....	120-120	—	—	—	—	—	—	
		2	3 c. c. (1-1)	.....	110-104-110	—	—	—	—	—	—	
		3	2 c. c. (23-1)	.....	.....	—	—	—	—	—	—	Spinal fluid—Baker.
		4	.....	.....	.....	—	—	—	—	—	—	Formation of clots with death of animal.
		5	" (20-1)	.....	.....	—	—	—	—	—	—	
6-27-11	Rabbit Q.	1	3 c. c. (1-1)	.....	104-106	—	—	—	—	—	—	
		2	3 c. c. (1-1)	.....	102-104	—	—	—	—	—	—	
		3	2 c. c. (20-1)	.....	.....	100-88-116	—	—	—	—	—	Spinal fluid—Baker.
		4	2 c. c. (20-1)	.....	92-74-100	—	—	—	—	—	—	No urine obtained.
		5	.....	1/20 gm.	96-88-110	—	—	—	—	—	—	
7-31-11	Rabbit R.	1	2 c. c. (20-1)	.....	110-116	—	—	—	—	—	—	
		2	2 c. c. (20-1)	.....	98-120	—	—	—	—	—	—	
		3	1/20 gm.	.....	—	—	—	—	—	—	—	Spinal fluid—Baker.
		4	2 c. c. (20-1)	.....	64-80	—	—	—	—	—	—	Spinal fluid, ox.
8-1-11	Rabbit S.	1	2 c. c. (20-1)	.....	.....	124-92-136	—	—	—	—	—	
		2	2 c. c. (20-1)	.....	110-64-194	—	—	—	—	—	—	
		3	1/20 gm.	.....	—	—	—	—	—	—	—	
		4	1/20 "	.....	94-104	—	—	—	—	—	—	
8-2-11	Rabbit T.	1	2 c. c. (20-1)	.....	64-80	—	—	—	—	—	—	
		2	2 c. c. (20-1)	.....	—	—	—	—	—	—	—	
		3	2 c. c. (20-1)	1/20 gm.	—	—	—	—	—	—	—	Vent. fluid—Holtzman.

## PROTOCOLS—CONTINUED

Date	Case	Injections			Blood pressure effects—mm. Hg.				Urine		Remarks	
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
8-8-11	Rabbit U.	1	2 c. c. (20-1)	2 c. c. (20-1)		130-136			128-110-140	+	—	Vent. fluid—Norris.
		2				1/20 gm.			142-120-162	—	—	
		3										
8-9-11	Rabbit V.	1	2 c. c. (20-1)	2 c. c. (20-1)					112-96-116	+	—	“ “ “
		2							98-78-98	+	—	
		3				1/20 gm.				—		
8-13-11	Dog W.	1				1/20 gm.			116-126			
		2				1/20 "				—	—	
		3				1/20 "			110-104-124	—	+	
8-14-11	Dog X.	1	2 c. c. (20-1)	2 c. c. (20-1)					114-98-126	—	+	“ “ “
		2								—	—	
		3				1/10 gm.			124-114-126	—	—	
		4				2 c. c. (20-1)			116-114-134	—	—	
8-15-11	Dog Y.	1	4 c. c. (20-1)				160-166			—	+	“ “ “
		2					160-210			—	+	Only few c. c. urine obtained.
		3				1/10 gm.				—	+	
		4	2 c. c. (40-1)			1/10 "			152-170	—	+	
		5							158-168	—	+	
8-16-11	Dog Z.	1	2 c. c. (20-1)						154-174	—	+	
		2				1/10 gm.				110-106-122	+	—
		3				2 c. c. (20-1)				115-62-178	—	—
		4								112-112-122	—	—
8-17-11	Dog A-2.	1	2 c. c. (20-1)	2 c. c. (20-1)						112-100-126	—	+
		2									—	Spinal fluid—Anderson.
		3				1/10 gm.					—	Only few drops of urine.
8-18-11	Dog B-2.	1	2 c. c. (4-1)								—	Spinal fluid—Hall.
		2	" (20-1)								—	" Stickley.
		3				2 c. c. (20-1)					—	50 c. c. of urine in bladder at end of experiment, 1.6% sugar.
		4									—	
		5				1/10 gm.					—	
		6				1/10 "					—	
		7				2/10 "					—	
11-24-11	Dog C-2.	1	3 c. c. (13-1)							72-60-84	—	Spinal fluid—Kurtz.
		2	" (13-1)							70-66-80	—	Suppression of urine.
		3				3 c. c. (13-1)					—	
		4								42-44	—	
		5								50-32-54	—	
11-27-11	Dog D-2.	1	3 c. c. (13-1)								—	Spinal fluid, ox.
		2	" (13-1)								—	Spinal fluid=Holtzwig.
		3	" (13-1)								—	Spinal fluid, ox.
		4				3 c. c. (13-1)					—	Suppression of urine.
		5								66-40-66	—	
		6									—	
		7									—	
11-28-11	Dog E-2.	1	3 c. c. (13-1)							94-50-94	—	Spinal fluid, ox.
		2	" (26-1)							60-66	—	Spinal fluid=Holtzwig.
		3				3 c. c. (26-1)				66-40-66	—	Spinal fluid, ox.
		4									—	Suppression of urine.
		5								70-50	—	
		6								64-74	—	
		7								68-78	—	
12-4-11	Rabbit F-2	1	2 c. c. (20-1)							—	+	Spinal fluid, ox.
		2				2 c. c. (20-1)				—	++	Spinal fluid—Morlock.
		3									++	
		4	2 c. c. (20-1)			1/20 gm.					—	
12-12-11	Dog G-2.	1	4 c. c. (20-1)							92-84-110	+	Ox-Alc. filtrate.
		2	" (20-1)							98-94-118	++	Ox-Alc. ppt.
		3								82-70-138	—	Alc. filtrate.
		4									—	Alc. ppt.
		5									—	
		6				4 c. c. (20-1)					—	
		7									—	
12-18-11	Dog H-2.	1	" (20-1)							104-44-104	+	
		2	4 c. c. (20-1)							96-80-96	++	
		3								86-62-68	—	
		4								96-114	—	
		5								80-58-80	—	
		6									—	
		7									—	
12-19-11	Dog I-2.	1	" (20-1)							60-50-52	—	Spinal fluid, ox.
		2	4 c. c. (20-1)							55-24-72	—	No urine chart.
		3									—	
		4									—	
		5									—	
		6									—	
		7									—	
12-19-11	Dog J-2.	1	" (20-1)							102-94-114	—	No urine chart.
		2	4 c. c. (20-1)							80-78-102	—	
		3	" (20-1)								—	
		4									—	
		5									—	
		6									—	
		7									—	
12-20-11	Dog K-2.	1	2 c. c. (20-1)				138-130-136			—	—	Ox-Alc. ppt.
		2	" (20-1)				128-126			—	—	Ox-Alc. filtrate.
		3	" (20-1)							126-120-136	+	
		4								—	—	
		5								—	—	
		6								—	—	
		7								—	—	
12-27-11	Dog N-2.	1	4 c. c. (20-1)							102-80-120	+	“ “ “
		2	" (20-1)							116-54-140	+	“ “ “
		3								—	—	
		4								—	—	
		5								—	—	
		6								—	—	
		7								—	—	

## PROTOCOLS—CONTINUED

Date	Case	Injections			Blood pressure effects—mm. Hg.				Urine		Remarks	
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
12-2-11	Dog O-2.	1	4 c. c. (20-1)	.....	.....	.....	.....	140-84-140	.....	+	+	Spinal fluid, ox.
		2	.....	004 Choline.	.....	.....	.....	122-84-130	.....	+	+	
		3	.....	001 Atropine.	.....	.....	.....	118-100-124	.....	+	+	
		4	4 c. c. (20-1)	.....	.....	.....	102-104	.....	104-56-122	—	++	
		5	.....	004 Choline.	.....	.....	.....	.....	94-54-124	+	++	
		6	4 c. c. (20-1)	.....	1/10 gm. P.	.....	.....	106-60-90	.....	+	++	
		7	.....	.....	1/10 " P.	.....	.....	100-124	.....	—	++	
		8	.....	.....	1/10 " P.	.....	.....	106-118	.....	—	+++	
		9	.....	.....	1/1- " P.	.....	.....	.....	.....	—	+++	
1-3-12	Dog P-2.	1	4 c. c. (20-1)	.....	.....	120-122	.....	.....	.....	+	—	Spinal fluid, ox.
		2	4 c. c. (20-1)	.....	.....	.....	118-54-124	.....	112-78-124	+	—	
		3	.....	004 Choline.	.....	.....	.....	.....	.....	+	—	
		4	.....	.....	1/10 gm. P.	.....	106-180-98	.....	.....	+	+	
		5	.....	001 Atropine.	.....	84-94	.....	100-58-104	.....	—	+	
		6	4 c. c. (20-1)	.....	.....	.....	.....	96-56 96	.....	—	+	
		7	4 c. c. (20-1)	.....	004 Choline.	102-105-102	.....	94-116-100	.....	—	++	
		8	.....	.....	1/10 gm. P.	.....	92-108-98	.....	.....	—	++	
		9	.....	.....	1/10 " P.	.....	.....	.....	.....	—	+++	
1-9-12	Dog Q-2.	1	.....	7 gld. A.	.....	.....	.....	148-98-168	—	—	+	Parke Davis. Armour.
		2	.....	7 " P. I.	.....	.....	.....	142-120-174	—	—	++	
		3	.....	7 " P.	.....	.....	.....	150-114-166	++	++	+++	
		4	.....	2/10 gm. P.	136-134	.....	.....	.....	+	+++	+++	
		5	.....	2/10 " P.	.....	128-death.	.....	.....	—	—	—	
1-22-12	Dog R-2.	1	Ash 4 (10-1)	.....	.....	134-148	.....	?	—	—	—	Spinal fluid—Perkins. " " Ginn.
		2	4 c. c. (10-1)	.....	.....	134-134	.....	—	+	—	—	
		3	.....	1/10 gm. Ant.	.....	.....	120-68-124	—	—	—	—	
		4	.....	1/10 " P. I.	.....	.....	116-80-120	—	—	—	—	
		5	.....	1/10 " P.	.....	122-30-98	—	—	—	—	—	
		6	.....	1/10 " P.	.....	74-68-104	—	—	—	—	—	
1-24-12	Dog S-2.	1	Ash 4 (10-1)	.....	.....	94-108	.....	—	—	—	—	Ash—Perkins fluid. Spinal fluid—Perkins.
		2	4 c. c. (10-1)	.....	.....	96-108	.....	—	+	—	—	
		3	.....	1/10 gm. Ant.	.....	.....	110-76-120	—	—	+	—	
		4	.....	1/10 " P. I.	.....	.....	116-94-144	—	—	+	—	
		5	.....	1/10 " P.	.....	116-150	—	—	—	—	++	
		6	.....	1/10 " P.	.....	124-118-134	—	—	—	—	++	
1-29-12	Dog T-2.	1	Ash 4 (10-1)	.....	.....	152-144	.....	—	—	—	—	Ox fluid—Ash. Suppression of urine.
		2	4 c. c. (10-1)	.....	.....	144-60-156	.....	—	—	—	—	
		3	.....	1/10 gm. Ant.	.....	.....	138-130-158	—	—	—	—	
		4	.....	1/10 " P. I.	.....	120-156	—	—	—	—	—	
		5	.....	1/10 " P.	.....	94-68-98	—	—	—	—	—	
1-31-12	Dog U-2.	1	.....	1/10 gm. Ant.	.....	140-156	—	—	—	—	—	Posterior lobe removal. Suppression of urine.
		2	.....	1/10 " P.	.....	130-152	—	—	—	—	—	
		3	.....	1/10 " P.	.....	136-118	—	—	—	—	—	
2-5-12	Dog V-2.	1	Ash 4 (10-1)	.....	.....	144-128-162	—	—	—	—	—	Ox fluid—Ash. Spinal fluid, ox.
		2	4 c. c. (10-1)	.....	.....	150-76-136	—	—	—	—	—	
		3	.....	1/10 gm. Ant.	.....	138-110-144	—	—	—	—	—	
		4	.....	1/10 " P. I.	.....	130-108-150	—	—	—	—	—	
		5	.....	1/10 " P.	.....	126-88-126	—	—	—	—	—	
		6	.....	1/10 " Ant.	.....	106-96-126	—	—	—	—	—	
		7	.....	1/10 " P.	.....	126-104-136	—	—	—	—	—	
2-12-12	Dog W-2.	1	Ash 4 (10-1)	.....	.....	156-150-176	—	—	—	—	—	No urine. Ox fluid—Ash.
		2	4 c. c. (10-1)	.....	.....	174-90-190	—	—	—	—	—	
		3	.....	2/10 gm. Ant.	.....	170-130-190	—	—	—	—	—	
		4	.....	2/10 " P. I.	.....	170-118-200	—	—	—	—	—	
		5	.....	2/10 " P.	.....	172-102-186	—	—	—	—	—	
		6	.....	2/10 " P.	.....	192-174-192	—	—	—	—	—	
		7	.....	2/10 " P.	170-176	—	—	—	—	—	—	
4-1-12	Dog X-2.	1	.....	Sugar sol.	124-124	—	—	—	—	—	—	No urine. Spinal fluid, ox. " " "
		2	.....	"	124-126	—	—	—	—	—	—	
		3	5 c. c. (20-1)	.....	124-120-122	—	—	—	—	—	—	
		4	(20-1)	.....	118-110-122	—	—	—	—	—	—	
		5	.....	Sugar sol.	118-118	—	—	—	—	—	—	
		6	.....	2/10 gm. Ant.	—	—	—	—	—	—	—	
		7	.....	2/10 " P. I.	—	—	—	—	—	—	—	
		8	.....	2/10 " P.	—	—	—	—	—	—	—	
		9	.....	2/10 " P.	108-40-108	—	—	—	—	—	—	
		10	5 c. c. (40-1)	.....	108-death	—	—	—	—	—	—	
4-2-12	Dog Y-2.	1	.....	2/10 gm. Ant.	120-84-120	—	—	—	—	—	—	No urine.
		2	.....	2/10 " P. I.	112-70-104	—	—	—	—	—	—	
		3	.....	2/10 " P.	110-36-78	—	—	—	—	—	—	
		4	5 c. c. (40-1)	.....	—	—	—	—	—	—	—	
4-3-12	Cat Z-2.	1	.....	1/10 gm. Ant.	132-56-126	—	—	—	—	—	—	Spinal fluid, ox.
		2	.....	1/10 " P.	125-58-94	—	—	—	—	—	—	
		3	.....	1/10 " P.	105-46-58	—	—	—	—	—	—	
5-23-12	Dog A-3.	1	.....	Colloid.	146-106-146	—	—	—	—	—	—	Fresh gland preparation. No urine.
		2	.....	1/2 gld. Ant.	152-death	—	—	—	—	—	—	
5-24-12	Dog B-3.	1	.....	2/2 " Ant.	90-84-88	—	—	—	—	—	—	Fresh gland preparation. No urine.
		2	.....	1/2 " Ant.	86-80-86	—	—	—	—	—	—	
		3	.....	1/2 " P.	88-136-98	—	—	—	—	—	—	—
5-24-12	Dog C-3.	1	.....	1/2 " Whole	90-96-88	—	—	—	—	—	—	Fresh gland preparation. No urine.
		2	.....	1/2 " P.	88-100-80	—	—	—	—	—	—	
		3	.....	5/10 gm. Ant.	80-92	—	—	—	—	—	—	
		4	.....	5/10 " P.	82-62-110	—	—	—	—	—	—	

## PROTOCOLS—CONTINUED

Date	Case	Injections			Blood pressure effects—mm. Hg.				Urine		Remarks	
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
5-29-12	Dog D-3.	1	.....	.....	3/10 gld. A.	.....	.....	.....	180-80-150	.....	.....	Fresh gland preparation. Suppression of urine.
		2	.....	.....	3/10 " P.	.....	.....	.....	130-90-176	.....	.....	
		3	.....	.....	1 gld. Whole	80-196	.....	.....		.....	.....	
		4	.....	.....	Choroid.	126-144	.....	.....		.....	.....	
		5	.....	.....	Pineal.	.....	184-98-134	.....		.....	.....	
		6	.....	.....	3/10 gld. P.	130-190	.....	.....		.....	.....	
		7	.....	.....	.....	.....	.....	.....	144-122-166	.....	.....	
		8	4 c. c. (8-1)	.....	1 " P.	.....	.....	.....	156-106-170	.....	.....	Spinal fluid, ox.
		9	.....	(3-1)	.....	.....	.....	.....	162-116-166	.....	.....	" " "
		10	.....	.....	3/10 gms. P.	.....	.....	.....	188-100-164	.....	.....	
5-31-12	Dog E-3.	1	.....	.....	3/10 gld. A.	.....	146-100-144	.....	.....	.....	.....	
		2	.....	.....	3/10 " P.	146-186-146	.....	.....	.....	.....	.....	
		3	.....	.....	3/10 " W.G.	.....	.....	.....	120-100-170	.....	.....	
		4	.....	.....	3/10 " A.	.....	.....	.....	134-124-148	.....	.....	
		5	.....	.....	3/10 " P.	120-170	.....	.....		.....	.....	
		6	.....	.....	3/10 " W.G.	.....	.....	.....	144-118-168	.....	.....	
		7	4 c. c. (5-1)	.....	.....	.....	.....	.....	136-110-142	.....	.....	Spinal fluid, ox.
		8	.....	(20-1)	.....	.....	.....	.....	126-98	.....	.....	" " "
		9	.....	.....	3/10 gms. P.	98-100	.....	.....		.....	.....	
		10	.....	.....	3/10 " A.	.....	108-98-114	.....		.....	.....	
6-3-12	Dog F-3.	1	.....	.....	3/10 gld. A.	.....	.....	.....	106-72-112	.....	.....	Suppression of urine.
		2	.....	.....	3/10 " P.	.....	.....	.....	130-104-140	.....	.....	
		3	.....	.....	3/10 " W.G.	.....	.....	.....	110-80-120	.....	.....	
		4	3 c. c. (20-1)	.....	.....	.....	.....	.....	88-56-116	.....	.....	Spinal fluid, ox.
		5	.....	.....	3/10 gms. A.	.....	.....	.....	112-80-120	.....	.....	" " "
		6	.....	.....	3/10 " P.	.....	.....	.....	106-78-152	.....	.....	
		7	3 c. c. (10-1)	.....	.....	98-128	.....	.....		.....	.....	
7-12-12	Dog G-3.	1	.....	.....	1 gld. Ant.	.....	.....	.....	112-54-138	.....	.....	
		2	.....	.....	1 " W. G.	.....	.....	.....	124-32-164	.....	.....	
		3	.....	.....	1 " P.	124-148	.....	.....		.....	.....	
		4	.....	.....	1 " P.	.....	.....	.....	124-118-170	.....	.....	
		5	.....	.....	1.8 gld. P.	.....	.....	.....	114-68-142	.....	.....	
		6	.....	.....	.....	.....	.....	.....		.....	.....	
7-16-12	Dog H-3.	1	5 c. c. (1-1)	.....	.....	.....	84-104	.....	98-56-70	.....	.....	
		2	2 c. c. (7-1)	.....	.....	.....	74-72	.....		.....	.....	Spinal fluid—Truslow.
		3	5 c. c. (4-1)	.....	.....	1 gld. Ant.	76-80	.....		.....	.....	Spinal fluid, ox.
		4	.....	.....	1 " P.	86-144	.....	.....		.....	.....	Fresh gland, no urine.
		5	.....	.....	1 " W. G.	.....	.....	.....	114-68-142	.....	.....	
		6	.....	.....	.....	.....	.....	.....		.....	.....	
7-17-12	Dog I-3.	1	5 c. c. (1-1)	.....	.....	.....	80-116-80	.....	.....	.....	.....	
		2	.....	(7-1)	.....	.....	64-98	.....	.....	.....	.....	Spinal fluid—Truslow.
		3	.....	(4-1)	.....	91-100	.....	.....	.....	.....	.....	Spinal fluid, ox.
		4	.....	.....	1 gld. Ant.	92-96	.....	.....	.....	.....	.....	Spinal fluid—Truslow.
		5	.....	.....	1 " P.	90-126	.....	.....	.....	.....	.....	Fresh gland preparation, no urine.
		6	.....	.....	1 " W. G.	108-122	.....	.....	.....	.....	.....	
		7	.....	.....	1 " P.	108-126	.....	.....	.....	.....	.....	
7-26-12	Dog J-8.	1	5 c. c. (1-1)	.....	.....	82-74-86	.....	90-72-56	.....	.....	.....	Vent. fluid—Gannon.
		2	.....	(1-1)	.....	.....	84-82-90	.....	.....	.....	.....	Spinal fluid, ox.
		3	.....	(4-1)	.....	.....	.....	88-76-98	.....	.....	.....	Vent. fluid—Gannon.
		4	.....	(20-1)	.....	1 gld. Ant.	86-96	.....	.....	.....	.....	Spinal fluid, ox.
		5	.....	.....	1 " P.	86-death.	.....	.....	.....	.....	.....	Fresh preparation.
		6	.....	.....	.....	.....	.....	.....	.....	.....	.....	
8-5-12	Dog K-3.	1	3 c. c. (20-1)	.....	.....	.....	134-110-138	.....	120-94-138	+	?	Spinal fluid, ox.
		2	.....	(20-1)	.....	1 gld. Ant.	106-86-114	.....	.....	+	+	Spinal fluid—Waltz.
		3	.....	.....	1 " P.	112-88-102	.....	.....	+	+	+	Fresh preparation.
		4	.....	.....	1 " W. G.	104-80-114	.....	.....	+	+	+	
		5	.....	.....	1 c. c. Pitu.	110-120	.....	.....	+	+	+	
		6	.....	.....	2 " "	108-120	.....	.....	+	+	+	
		7	.....	.....	1/2 gld. P.	104-82-100	.....	.....	+	+	+	
		8	.....	.....	.....	.....	.....	.....	.....	.....	.....	
8-8-12	Dog L-3.	1	5 c. c. (20-1)	.....	.....	.....	94-60-102	.....	.....	+	+	Spinal fluid, ox.
		2	.....	(20-1)	.....	1 gld. Ant.	98-84-124	.....	.....	+	+	Spinal fluid—Wolf.
		3	.....	.....	1 gld. Ant.	100-death.	.....	.....	—	+	+	Fresh preparation.
8-8-12	Dog M-8.	1	5 c. c. (20-1)	.....	.....	.....	.....	.....	98-76-126	+	—	Spinal fluid, ox.
		2	.....	(20-1)	.....	1 gld. Ant.	80-48-100	.....	.....	++	—	Spinal fluid—Causey.
		3	.....	.....	1 gld. Ant.	88-death.	.....	.....	—	—	—	
8-9-12	Dog N-8.	1	20 c. c. Lockes	.....	.....	78-84	.....	.....	.....	.....	.....	
		2	20 c. c. (1-1)	.....	1 gld. P.	88-96	.....	.....	.....	.....	.....	
		3	.....	.....	1 " P.	96-140	.....	.....	.....	.....	.....	
		4	.....	.....	1 " W. G.	94-118	.....	.....	.....	.....	.....	
		5	.....	.....	1 " Ant.	102-98-108	.....	.....	.....	.....	.....	
		6	.....	.....	1 c. c. Pitu.	94-106	.....	.....	.....	.....	.....	
		7	.....	.....	1 " "	96-128	.....	.....	.....	.....	.....	
8-9-12	Dog O-3.	1	5 c. c. (20-1)	.....	.....	66-82	.....	.....	.....	.....	.....	
		2	.....	(20-1)	.....	66-78	.....	.....	.....	.....	.....	
		3	.....	.....	1 gld. Ant.	76-46	.....	.....	.....	.....	.....	Vent. fluid—Levenstein.
		4	.....	.....	1 " P.	65-56-64	.....	.....	.....	.....	.....	Fresh gland.
		5	.....	.....	1 " W. G.	.....	.....	.....	52-36-68	.....	.....	
		6	.....	.....	1 c. c. Pitu.	.....	.....	.....	.....	.....	.....	
		7	.....	.....	1 " "	58-62-60	.....	.....	.....	.....	.....	
		8	.....	.....	5 " "	56-56	.....	.....	.....	.....	.....	
		9	.....	.....	5 " "	56-64	.....	.....	.....	.....	.....	

parts of the gland. Record 23 shows the hæmodynamic reactions in a cat in which only depressor responses could be obtained from different portions of gland injected. That the effects of injections of cerebrospinal fluid, ox fluid and posterior lobe may be practically identical is shown by Record 24, in which we have the curves superimposed on one another. On the other hand, Records 25 to 33 show a series of unusually consistent results obtained by repeated injections of hypophyseal extract and of spinal fluid. Here there is well demonstrated (1) the depressor effect of the anterior lobe, (2) the pressor effect of the posterior lobe, (3) the neutralization of these effects in the whole gland injection, (4) the gradual diminution of pressor effects on repeated injections, (5) the depressor effect of concentrated spinal fluid. One must add also that there are many varieties of records between the extremes herein presented and that practically each one of the substances injected, at some time or other, gave marked depressor effects resulting in the death of the animal. As a rule, however, it may be stated that an animal reacting poorly for one injection responded also poorly to the other substances and that the few animals under chlortetone reacted less decisively than those under ether.

A statistical study of some 305 injections and tracings is given in Table 2, furnishing the opportunity of a more quanti-

TABLE 2.—SUMMARY OF HÆMODYNAMIC EFFECTS OF INJECTIONS OF EXTRACTS

	No.	Negative	Depressor	Pressor	Depressor and pressor	Combined dep.-pres. average
Spinal fluid.....	120	15-12.5% {	30-25 % av.-40 mm. 5 deaths.	25-20.9 % av.-17 mm.	50-40 % 25-19 mm.	30-18 mm.
Art. spl. fluid.....	29	17-59. % {	6-20.7 % av.-16 mm. 1 death.	1-3.4 % av.-10 mm.	5-17 % 16-18 mm.	16-18 mm.
P. lobe .....	102	3-2.0% {	10-18.6 % av.-32 mm. 3 deaths.	46-45 % av.-33 mm.	34-33.3 % 26-23 mm.	28-34 mm.
Ant. lobe .....	36	5-14. % {	14-39 % av.-34 mm. 4 deaths.	6-16.6 % av.-14 mm.	11-30.6 % 28-15 mm.	31-18 mm.
Pars-intermedia .....	8	0 {	0 .....	1-12 % av.-30 mm.	7-88 % 23-22	23-23 mm.
Whole gland.....	11	0 {	1-9 % av.-13 mm.	4-35 % av.-16.	6-55 % 19-18.4	18-17 mm.

tative study of these qualitative reactions done under uniform conditions.

Quantitatively, the averages of the combined pressor effect of spinal and artificial fluid are about the same, while the depressor effect of the spinal fluid is about twice that of artificial fluid; on the other hand the posterior lobe injection while accompanied by a depressor effect of short duration, is essentially a pressor effect both from the height of blood pressure curve and from the duration of the same. Just how much of the pressor effect of the depressor-pressor sequence of spinal and artificial fluid is due to the over-reaction of the animal to the primary depressor effect is difficult to state, but the fact that it is constant when occurring alone and in the sequence, in both fluids, seems to indicate that it most probably is associated with the inorganic content of these fluids and not due

to any definite, specific, blood pressure raising entity. This latter statement is confirmed by the disappearance of the marked depressor effect on injection of the ash from an equal bulk of concentrated fluid; this is seen graphically in Records 34-35. These data seem to indicate that the predominating hæmodynamic substance in concentrated spinal fluid is a depressor one rather than a pressor one as would be indicated by the presence of a posterior lobe secretion.

4. *Diuretic Effects.*—A study of the diuretic effects of the injections is given in Table 3.

TABLE 3.—SUMMARY OF URINARY EFFECTS OF INJECTION OF EXTRACTS

	Diuresis			Glycosuria		
	No.	Positive	Per cent	No.	Positive	Per cent
Spinal fluid.....	83	57	79	95	44	46
Art. spl. fluid.....	21	15	71	28	13	46
P. lobe .....	71	15	21	69	59	86

A definite diuresis occurs after most of the injections of spinal and artificial fluid. This is due most probably to the hypertonicity of the solution injected. With the posterior

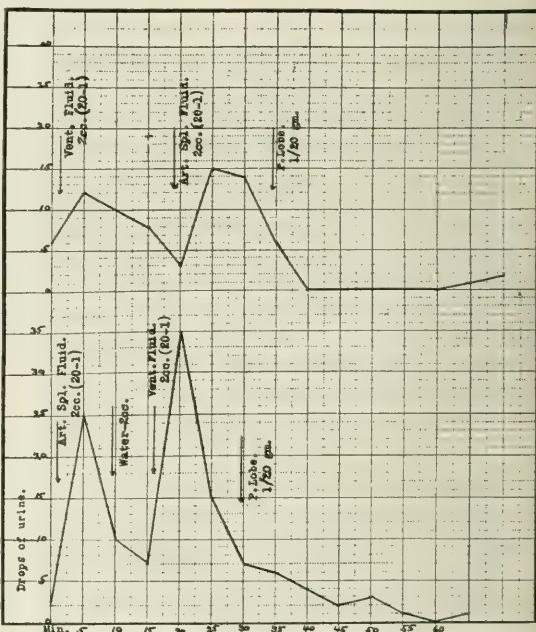


CHART I.—Showing diuretic effects of spinal fluids and anti-diuretic effects of the posterior lobe extract in dogs.

lobe injection, however, the slight transient diuresis which may occur is usually followed by a definite decrease in the urinary outflow which persists for a longer time so that, concentrated solutions injected subsequently are unaccompanied

by the usual diuretic effect. This anti-diuretic effect is quite marked and is contrary to the observations of Herring<sup>8</sup> regarding the diuretic effects of the posterior lobe and seem to confirm those recently made by Motzfeldt,<sup>9</sup> who found a definite decrease in the urinary outflow as a sequence to posterior lobe injections. Chart I shows the anti-diuretic effects of posterior lobe injections in contrast to the diuretic effect of concentrated cerebrospinal and artificial fluids.

**5. Glycogenic Effect.**—A study of the production of glycosuria from the above injections is also given in Table 3. Exact observations of this reaction were accompanied by considerable difficulty owing to the fact that the first appearance of sugar in the urine invalidated to a certain extent the correctness of interpreting the results of subsequent injections. However, by making tests of a quantitative nature some definite conclusion could be obtained. It is well to note that the glycosuria was produced to about the same percentage of frequency in both spinal and artificial injections, while the posterior lobe injection was almost invariably followed by a glycosuria or increase in urinary sugar contents. The production of glycosuria under such conditions occurred more readily in rabbits than in dogs.

#### SUMMARY

From the foregoing data it is evident that:

1. Concentrated cerebrospinal fluid, human and bovine, when injected intravenously into rabbits and dogs is accompanied by a depressor-pressor sequence similar to that produced by equal concentrates of "artificial spinal fluid," a solution isotonic to normal spinal fluid. The small pressor component is quantitatively equal to that of the isotonic solution and is due probably to the over-reaction of the animal to the depressor effect of the concentrated inorganic sodium and potassium salts. The augmented depressor effect of the cerebrospinal fluid is due to the presence of a small amount of organic material in solution, making the effect essentially a depressor one instead of a pressor one indicative of the posterior lobe secretion.

2. Diuresis usually accompanied the injection of concentrated spinal and artificial fluid and is due most probably to hypertonicity of the salt solution. Injections of the posterior lobe extract were usually followed by an anti-diuretic effect, leading to suppression of urine in a large number of cases.

3. Glycosuria follows the injection of concentrated spinal and artificial fluid in about the same number of cases and is most probably associated with the high concentration of the inorganic salts. It is more common as a sequence to injections of posterior lobe extract and is usually greater in amount. This glycosuric effect is seen more frequently in rabbits than in dogs.

#### NATURE OF DEPRESSOR SUBSTANCE

Schaefer and Oliver in their pioneer researches upon the gland attributed the haemodynamic effect to the whole gland. Howell<sup>10</sup> in 1898 showed that this property was characteristic of the posterior lobe and this finding was confirmed by Schae-

fer and Vincent,<sup>11</sup> in 1899, who demonstrated an active depressor substance soluble in alcohol and a pressor substance in soluble in that reagent. Hamburger<sup>12</sup> in 1904 demonstrated the existence of a depressor and a pressor substance in the anterior lobe, but Schaefer and Herring<sup>13</sup> in 1906 failed to corroborate these findings. Cyon,<sup>14</sup> in 1907, investigated the depressor substance of the posterior lobe and thought that it might be similar to choline. Hamburger,<sup>15</sup> in 1910, repeated his work of 1904, getting identical results as previously, and questioned the method of preparation used by Schaefer and Herring. Lewis,<sup>16</sup> in 1911, found that the pars intermedia and nervosa have definite pressor effects and the pars anterior contained a depressor effect and a small pressor effect, the latter due most probably to its intimate contact with the intermedia. It was his opinion that the secretion was produced in the pars intermedia and given to the pars nervosa. In 1912, Engeland and Kutschner<sup>17</sup> drew attention to a substance obtained from the whole gland preparation which had the marked property of stimulating smooth muscle but had no effect upon the blood pressure. Herring,<sup>18</sup> in 1915, found no pressor substance in either anterior lobe or pars intermedia, but a definite pressor substance in the posterior lobe. He considered the substance discovered by Engeland and Kutschner to represent only one of the stages in the formation of the pressor secretion which was formed in the pars intermedia and given to the pars nervosa, undergoing changes there as characterized by changes in the hyaline bodies. There thus is seen to be marked confusion regarding the pressor and depressor effects of the various parts of the pituitary gland. This most probably is due to the fact that it is very difficult to make an absolute separation of the different structures of the gland and also because of the variability of the responses in the animal itself, as seen from the preceding records.

Examination of records of injection of concentrated cerebrospinal fluid, anterior and posterior lobes, pars intermedia and whole gland usually show a primary depressor effect followed by a pressor response of greater or less extent depending upon the part of the gland injected. The similarity of this depressor response is very striking and leads one to infer a common cause or origin for it. A quite similar depressor curve is also seen in tracings of injections of colloid material taken from the interlobar cleft and also from extracts of choroid plexus and pineal gland, as can be seen in Records 36-37.

Several definite conclusions are reached regarding this depressor substance.

**1. It is Common to All the Above-Named Extracts and Fluids.**—In spite of the greatest care used in separating the different parts of the pituitary gland, injections of these separated substances almost invariably give a depressor effect either as the whole or part of the reaction.

**2. Nature of Depressor Effect.**—This occurs as a marked vaso-dilator effect with marked fall in blood pressure. It is usually in the form of a primary fall and followed by a greater or less pressor effect. Depressor effect is usually of short duration. Injections showing pressor and depressor effects alone are rather unusual, the depressor and pressor sequence being

the usual reaction. The pressor effect is most marked in the posterior lobe and pars intermedia, whereas the depressor effect is most marked in the concentrated spinal fluid, human and bovine, and in the anterior lobe. Death from extreme depressor effects is noted in about 13 out of 305 injections. It followed injections of concentrated spinal fluid, anterior and posterior lobe, occurring often from a primary injection and also as a sequence to subsequent injections. In several cases death of the animal from continued depressor effect was prevented by the injection of adrenalin which caused a marked vaso-constrictor effect with rise in blood pressure and resumption of animal function. Records 38-39 indicate the depressor effect leading to a fatal outcome and one in which death was most probably prevented by the injection of adrenalin.

*3. Effect on Smooth Muscle.*—Several observations show that these substances have a definite stimulating effect on smooth muscle such as intestine, bladder and uterus. The uterus in several instances emptied itself of the foetus after injection of these extracts and eviscerated animals showed a moderate increase of peristalsis on injection.

*4. Solubility.*—This depressor substance evidently is soluble in water and in alcohol. Solutions of the evaporated alcoholic filtrates of both spinal fluid and posterior lobe, when injected into an animal, showed the identical depressor effect characteristic of concentrated spinal fluid and posterior lobe injections, while solutions of the alcoholic precipitate gave no appreciable effect in case of the spinal fluid and only a pressor effect on posterior lobe injections (See Records 40-41).

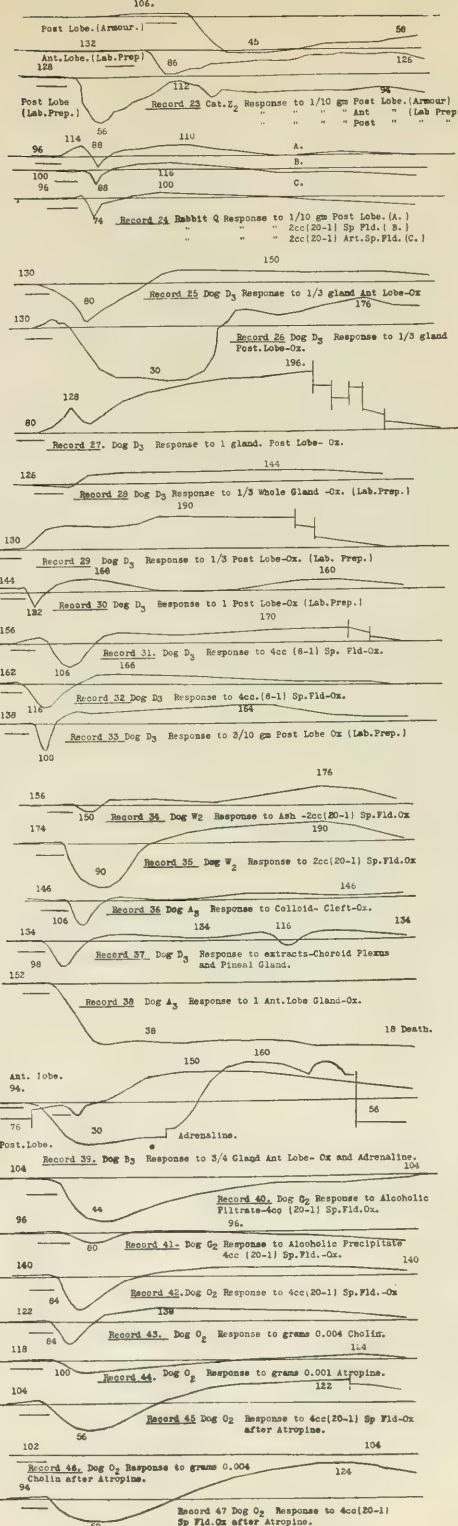
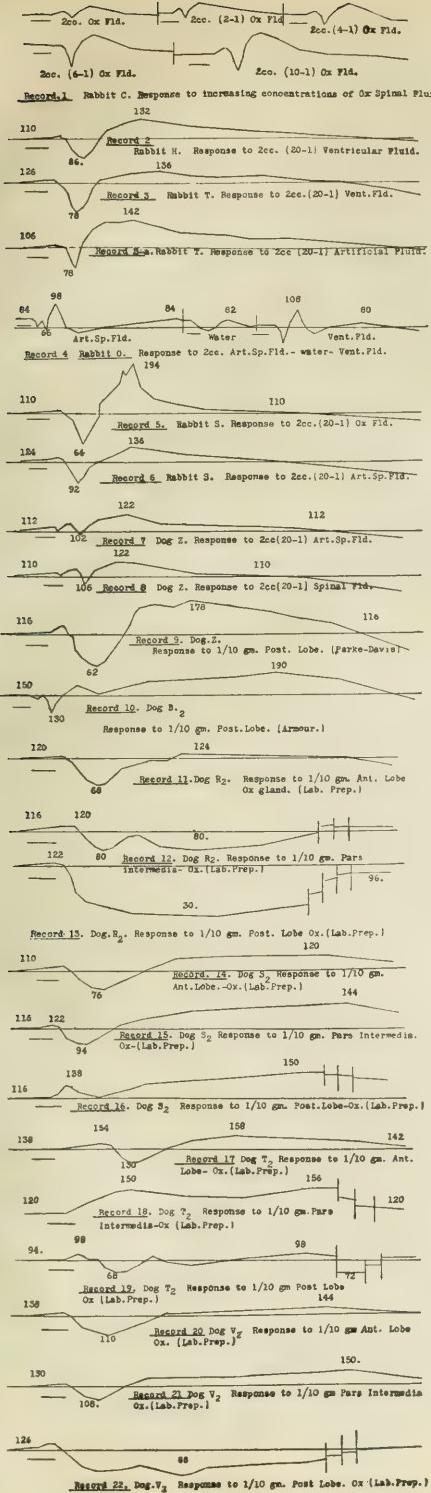
*5. Depressor Substance Not Choline.*—Choline is a substance produced in the decomposition or destruction of cell life and is physiologically demonstrated by showing a marked depressor effect when introduced into the body, a depressor effect which can be abolished by atropine. Records 42-47 demonstrate clearly the persistence of the depressor effect of the concentrated cerebrospinal fluid injections before and after the administration of atropine and the obliteration of the choline depressor effect after that injection.

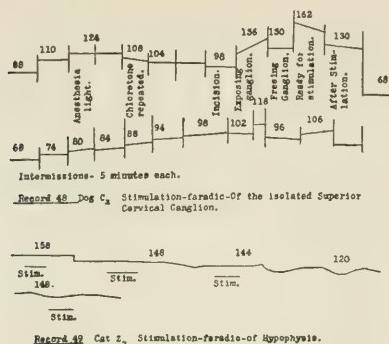
*6. Not Affected by Stimulation of the Gland.*—Weed, Cushing and Jacobson,<sup>13</sup> in 1913, demonstrated that glycosuria could be produced in animals with available glycogen by (1) direct stimulation of the hypophysis and (2) by stimulation of the superior cervical ganglion after the exclusion of all cephalad impulses; thus indicating the liberation of some substance, presumably of hypophyseal origin, causing glycogenolysis and glycosuria. Rabens and Lifschutz<sup>14</sup> in 1915, however, by using similar methods failed to get any evidence of an increase in the reducing power of the blood, as an index of such reaction, but in 1915 Keeton and Becht<sup>15</sup> and also Shamoff<sup>16</sup> in the same year, obtained glycosuria and an increase in the reducing power of the blood by a similar procedure and thus confirmed the original observations in that particular. If such stimulation increased the secretory activity of the gland, it seemed quite probable also that some additional haemodynamic reaction should result from the outpouring of the secretion either into the blood-stream or into the cerebrospinal fluid. Stimulation of the hypophysis directly

and of the isolated superior cervical ganglion gave the usual glycosuria but failed to show any special pressor or depressor effect except that which accompanied the manipulation of the gland, itself (See Records 48-49).

*7. Relation to Hypophysectomy.*—Ductless glands are generally supposed to elaborate some special substance or internal secretion necessary for the body economy and the conditions designated as hypo-activity and hyper-activity to be accompanied by essentially characteristic changes in the animal and in their reactions to the special specific substance involved. Consequently, it was thought advisable to see what special or altered effects the injections of concentrated spinal fluid, anterior and posterior lobe extracts, would have upon a "hypo" condition experimentally produced. Injections of cerebrospinal fluid, anterior and posterior lobe extracts, gave in hypophysectomized animals reactions not essentially different from those of normal animals nor did they elicit any suggestion of any special hypo- or hyper-sensitivity to the specific substance involved by the anterior or posterior lobe removal.

That tissue extracts on injection have haemodynamic power had been recognized many years ago; by Schaefer and Moore<sup>17</sup> in 1900 and again by Halliburton<sup>18</sup> in 1901, these two latter investigators differing as to whether it was a choline effect. In 1903 Vincent and Sheen<sup>19</sup> showed that typical depressor curves could be obtained from a variety of tissue extracts and concluded that all glandular structures and probably all animal tissue contained, in their extracts, a depressor and pressor substance. Since then similar effects have been demonstrated by many investigators. Since the discovery of Enriguez and Hallion,<sup>20</sup> in 1904, that a stimulant to intestinal musculature could be obtained from extracts of gastric and intestinal mucosa, there arose a group of substances descriptively named "peristaltic hormones" and "motilines," substances obtained from extracts of various tissues and exhibiting the symptom-complex of stimulating smooth muscle and at the same time having a marked depressor effect on blood pressure. The characteristic "peptone shock" of Witte's peptone and the depressor effect of *secretin* were such typical substances. Popielski,<sup>21</sup> in 1909, working on this depressor substance of peptone showed that its effect was not due to choline, which some time previously in 1908 had been identified by Lohman and Von Furth<sup>22</sup> and by Schwartz and Von Furth<sup>23</sup> as one of the depressor substances in tissue extract. He gave the name of "vaso-dilatin" to this hypothetical substance and also concluded that it was identical with the *secretin* of Bayliss and Starling.<sup>24</sup> In 1910 Dale and Laidlow<sup>25</sup> in describing the action of histamine-B. iminazolyl-ethylamine showed the similarity of its reaction to those of peptone, the "vaso-dilatin" of Popielski and to "histamine-like" substances in other tissue extracts. Barger and Dale in 1911<sup>26</sup> isolated the depressor substance from intestinal mucosa and concluded it to be histamine and that the "vaso-dilatin" of Popielski contained this same substance. In 1917 Abel and Pincoff<sup>27</sup> in working with some albumoses in pituitary extract, prepared from intestinal mucosa a water-soluble





substance indistinguishable in its effects from posterior lobe of the pituitary gland and inferred the presence of albumoses in both substances. They were led to infer that the motiline substance in the posterior lobe is not a hormone specific to the gland but a substance found in many other tissues, having its origin either in the tissues of the cell itself or as a product of its activity. Finally, in 1919, Abel and Kubota<sup>24</sup> isolated the active principal histamine from pituitary glands, intestinal mucosa, liver, muscle, peptone and other substances showing that it occurs widely in tissues and that the so-called "motiline," "peristaltic hormone," "vaso-dilatin," "histamine-like" substances, the plain muscle stimulant and blood depressor substance, were all identical and due to the specific substance "histamine."

Cerebrospinal fluid from its dual origin either from the choroid plexus as a specific secretion or selective filtrate, and as a source of drainage for the peri-vascular nerve spaces contains a small amount of organic matter in solution. Its properties and physiological reactions when injected intravenously as a concentrate are identical with those obtained from the various tissue extracts in general and with the depressor substance of the pituitary gland in particular; reactions now definitely demonstrated to be due to the active principal histamine which has been definitely isolated from these very tissues, histamine, an organic base, a product of the hydrolytic cleavage or decomposition of the protein molecule, most probably found in all animal tissues and secretions either as a part of the cell itself or incident to cell activity. The physiological reactions of the spinal fluid, a depressor effect, seem to be due to the depressor substance histamine and not to any specific secretion of the pituitary gland as was formerly contended.

#### CONCLUSIONS

1. Cerebrospinal fluid from human and bovine sources in concentration gives physiological reactions identical with those obtained from the injection of various tissue extracts, effects most probably due to the presence of histamine.

2. There is no definite evidence of the presence of a pressor substance in the cerebrospinal fluid suggestive of any posterior lobe secretion. It seems rather improbable that the

pituitary gland gives its secretion into the ventricles or into the cerebrospinal fluid.

3. All pituitary gland extracts show marked variability as far as their responses are concerned on intravenous injection. They all show a depressor effect common to the tissue extract. In general it may be said:

- (a) Anterior lobe exhibits depressor effect mainly.
- (b) Posterior lobe a moderate depressor followed by a specific pressor effect.
- (c) Pars intermedia has a small depressor, followed by a pressor effect.
- (d) Whole gland shows a neutralization of the depressor and pressor effects.
- (e) The posterior lobe secretion, if it is a specific secretion, is most probably produced in the pars intermedia and finds its way into the pars nervosa.

4. The posterior lobe extract on intravenous injections appears to have an antidiuretic rather than a diuretic effect.

5. Glycosuria is produced by intravenous injection of posterior lobe extract in a number of cases. This glycogenic effect is more marked in the rabbit.

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## BIOGRAPHY OF SIR WILLIAM OSLER

Lady Osler has requested me to prepare a biography of her husband, and I will be most grateful to anyone who chances to see this note, for any letters or personal reminiscences, or for information concerning others who may possibly supply letters.

Copies of all letters, no matter how brief, are requested, and if dates are omitted it is hoped that they may be supplied if possible.

If the originals are forwarded for copy they will be promptly returned.

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## EXPERIMENTAL OBSERVATIONS UPON THE URETERS, WITH ESPECIAL REFERENCE TO PERISTALSIS AND ANTI-PERISTALSIS

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The peristaltic movements of the ureters have been the object of repeated study. Thus Engelmann<sup>1</sup> in 1869 first described in detail the nature of the peristaltic contractions occurring in the living ureter. He observed that the contractions normally originate at the renal pelvis and proceed toward the bladder. He recorded the frequency of the peristaltic waves and the rate at which they travel. He also noted that the movements of the ureters are independent of one another. Finally, he watched the response of the ureteral musculature to mechanical and faradic stimulation and decided from these experiments that the contractions he had seen were independent of any intrinsic or extrinsic nerves, and that the

impulse to contract was conveyed directly from one muscle cell to another.

A further advance in our knowledge of the physiology of the ureter was made in 1881 by Sokoloff and Luchsinger.<sup>2</sup> They passed physiological salt solution through the ureter under varying pressures and noted the effect upon peristalsis. They observed that the greater the pressure of the fluid passing through the lumen of the ureter the more frequent and vigorous the peristaltic waves became.

Protopowpow<sup>3</sup> in 1897 investigated the finer structure of the ureter and demonstrated rich nerve plexuses and numerous ganglia in its wall. He showed that stimulation of the

splanchnic nerve causes increased ureteral peristalsis, whereas section of the same nerve inhibits peristalsis. He also observed that drugs are capable of stimulating or inhibiting the contractions of the ureteral musculature; thus, he noted that atropin first increases and then inhibits peristalsis.

In recent years the contractions of the ureter have been studied very carefully by the graphic method. Some investigators have obtained tracings of the movements of the ureter *in situ* while others have suspended rings or strips of excised musculature in warm, oxygenated Ringer's or Locke's solution. In this way Lucas,<sup>3</sup> Macht<sup>4</sup> and Satani<sup>5</sup> have graphically illustrated normal ureteral contractions and the effect of various drugs on them. They have been able to demonstrate that the ureter possesses, like other smooth muscle, sympathetic and autonomic nerve fibres which respond in a characteristic way to pharmacologic agents.

Satani,<sup>6</sup> in a recent paper, discusses the causes of ureteral contractions. He believes that the peristalsis of the ureter should be referred to several factors which act in cooperation. The most important of these are reflex stimulation of the motor nerves, direct mechanical distention of the ureteral musculature and a local reflex which is stimulated by the salts contained in the urine.

The object of our investigations has been to study the behavior of the ureter in the living animal under various experimental conditions. We have investigated primarily the peristaltic activity of the ureter after complete and partial ligation and, secondarily, the behavior of the ureter during the passage of glass beads from the renal pelvis to the bladder. The similarity between these experimental conditions and those encountered clinically in hydronephrosis and from ureteral calculi lend additional interest to the observations.

We have also repeated some experiments made by previous observers on regurgitation of fluid through the uretero-vesical orifice to determine what rôle peristalsis and antiperistalsis play in this phenomenon. Finally, we have made a few notes on the behavior of the ureter during experimental ureteral catheterization.

The results of our experiments may best be presented under the following headings:

1. The effect on peristalsis of partial and complete ligation of the ureter.
2. The behavior of the ureter during the passage of glass beads of various sizes.
3. The activity of the ureter during regurgitation of fluid from the bladder.
4. The behavior of the ureter during ureteral catheterization.

#### 1. THE EFFECT ON PERISTALSIS OF PARTIAL AND COMPLETE LIGATION OF THE URETER

Eight dogs and eleven rabbits were employed in these experiments. Of the dogs, three had one ureter completely ligated, five had one ureter partially so. In the rabbits, the

ureter was completely ligated in nine, and partially ligated in two animals.

The experiments consisted in operating on the animals under aseptic conditions, placing a partial or complete ligation about one ureter, preferably the left, allowing the animal to recover, and subsequently, after a period of days, weeks or months, opening the animal's abdomen and observing the peristaltic movements. Black silk thread was used when we tied off the ureter completely. For the partial ligation a narrow rubber band (2 mm. wide) was secured about the ureter so as partially to compress its lumen.

The results of these experiments can best be described by presenting some of the protocols in detail. In order to prevent needless repetition, however, no more protocols than necessary will be given and a brief summary at the end will incorporate the essential observations of all the experiments.

The following protocols illustrate the results of partial ligation:

RABBIT 19.—Male. Nov. 5, 1919. Partial ligation of the left ureter at the junction of its upper and middle thirds.

Dec. 9, 1919. A laparotomy under ether anaesthesia is performed. The left ureter is found moderately dilated above the rubber band. Below the band the ureter appears normal. The dilated portion of the ureter exhibits very active peristaltic movements. No spontaneous antiperistaltic waves are noted but on pinching the dilated ureter just above the band vigorous reversed peristaltic waves are elicited which pass from the point of stimulation up the ureter and disappear into the renal pelvis. On cutting through the dilated ureteral wall its musculature is found much thickened. A segment of the wall placed in warm, oxygenated Locke's solution contracts vigorously. The portion of the ureter below the band contracts with normal frequency and independently of the dilated ureter above. The opposite ureter shows contractions of normal rate and frequency.

Dog 3.—Female. Nov. 12, 1919. Left ureter partially ligated midway between the renal pelvis and the bladder.

Jan. 23, 1920. A laparotomy under ether is performed. The upper part of the left ureter is markedly dilated, the portion below the ligature appears normal. Vigorous peristaltic and anti-peristaltic waves are observed in the dilated ureter. There are from 4 to 6 waves per second. The peristaltic waves originate in the renal pelvis, and travel down the dilated ureter to the rubber band where most of them cease. A few, however, pass the constriction and proceed in a normal manner toward the bladder. The peristaltic movements are frequently interrupted by one or more reversed peristaltic waves which originate at the rubber band and travel upwards to the renal pelvis. On section the musculature of the ureter is found tremendously hypertrophied. Strips of the hypertrophied wall contract readily in warm, oxygenated Locke's solution.

Dog 5.—Male. Nov. 14, 1919. Left ureter partially ligated 6 cm. above the bladder.

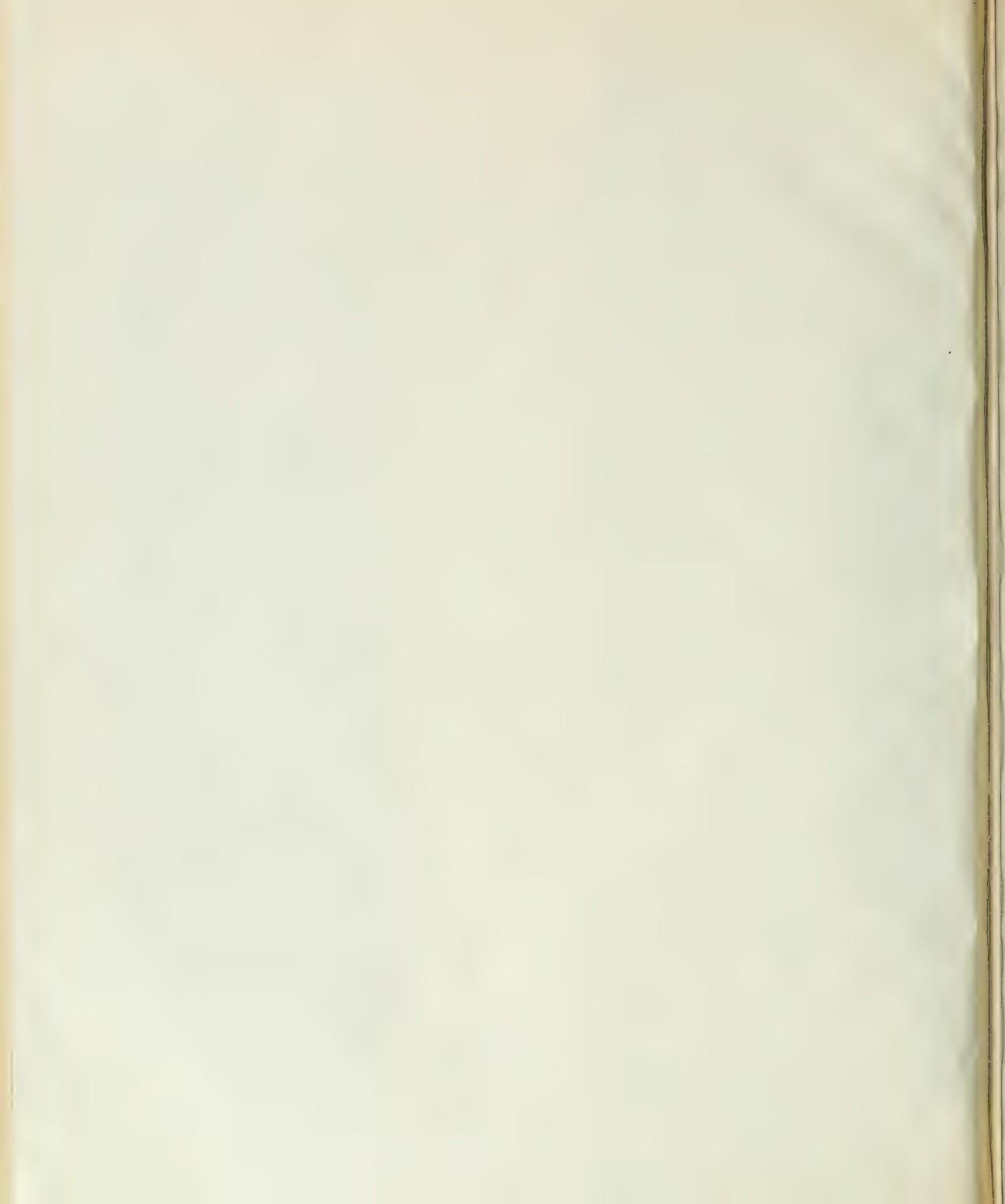
Feb. 9, 1920. A laparotomy under ether is performed. A well-marked hydroureter and hydronephrosis are encountered. Vigorous but rather infrequent peristaltic contractions of the ureter are observed with now and then a wave in the reverse direction. After aspiration of part of the fluid contained in the dilated ureter the contractions become more frequent and vigorous. On application of a crystal of barium chloride to the surface of the ureter a constriction ring is formed from which peristaltic waves proceed in both directions at regular intervals. The movements of the opposite ureter are normal.



FIG. 1.—Tracing of the contractions of a ureter which had been partially ligated two months previously. The effect of adrenalin (4 drops of a 1-10,000 solution) is shown.



FIG. 2.—Tracing from the same ureter showing the effect of one milligram of ergotoxin.



The following protocols illustrate the effect of complete occlusion of the ureter:

RABBIT 21.—Female. Nov. 5, 1919. Complete ligation of the left ureter in its middle with silk tie.

Nov. 17, 1919. A laparotomy is performed under ether. The left kidney and ureter are found markedly distended with fluid. No peristaltic movements are visible in the dilated ureter. Below the tie the ureter, which appears normal, is quiescent but contracts on stimulation. Peristaltic waves cannot be elicited by pinching the dilated ureter or applying a crystal of barium chloride to its surface. The barium chloride produces, however, a visible muscular constriction at the point of application. After the aspiration of about 10 c.c. of fluid from the ureter its musculature immediately commences to contract violently. Contraction waves are observed passing in both directions. On section the musculature is found to be greatly hypertrophied. The behavior of the ureter on the opposite side is normal.

DOG 6.—Male. Nov. 18, 1919. Complete ligation of the left ureter with silk thread about 8 cm. from the bladder.

Feb. 9, 1920. A laparotomy is performed under ether. An enormously dilated ureter and kidney are encountered. No peristaltic movements are visible in the dilated ureter nor can any be elicited on pinching the musculature. About one-half of the fluid contained in the ureter and kidney is aspirated whereupon peristaltic and anti-peristaltic contractions ensue of such violence and so frequently that the ureter appears to be performing vermiform movements. On refilling the ureter with salt solution these movements are brought to a standstill, to commence once more when the internal pressure is again relieved. On section the musculature of the ureter is found tremendously hypertrophied. Suspended in warm, oxygenated Locke's solution, rings of the musculature contract spontaneously. The ureter on the opposite side exhibits normal peristalsis.

#### SUMMARY

The results of these experiments upon partially and completely ligated ureters may be summarized as follows:

After partial ligation of the ureter its lumen increases in diameter and its musculature hypertrophies. When an incompletely ligated ureter is examined several weeks or months after operation, spontaneous peristalsis and frequently antiperistalsis is encountered. The peristaltic waves are always more vigorous and occasionally more frequent than those seen in the normal ureter. Vigorous antiperistaltic waves, if not spontaneously present, may be elicited by pinching. By the application of a crystal of barium chloride to the surface of the dilated ureter a constriction ring is formed from which peristaltic waves proceed in both directions. The ureter below the partial ligature exhibits normal spontaneous peristaltic contractions.

The lumen of the completely ligated ureter is somewhat larger than that of the partially ligated one. The musculature is also hypertrophied. The completely ligated ureter seldom shows any spontaneous peristaltic movements nor does it usually react to stimuli. When, however, part of the contained fluid is released, violent peristaltic and antiperistaltic movements commence, which are in no way distinguishable from those observed in the partially ligated ureter.

Bands of muscle from both partially and completely ligated ureters contract vigorously when suspended in warm, oxygenated

Locke's solution. The action of drugs on these preparations can be readily studied.

Figs. 1 and 2 show the effect of adrenalin and ergotoxin upon excised rings of musculature from a hydroureter.

#### 2. THE BEHAVIOR OF THE URETER DURING THE PASSAGE OF GLASS BEADS

In these experiments four rabbits and nine dogs were used. Somewhat flattened and perforated glass beads were introduced aseptically into the pelvis of the left kidney through a small nephrotomy puncture wound. After a few days or weeks had elapsed the animal was again anesthetized, a laparotomy was performed and the behavior of the ureter observed. Beads of different sizes were employed ranging in diameter from 0.08 up to 0.25 inch (2-6 mm.).

The following protocols, arranged with reference to the increasing size of the beads used, describe our observations:

DOG 7.—Male. Dec. 2, 1919. Left lumbar incision. Introduction of 6 perforated glass beads having a mean diameter of 0.085 inch (slightly less than 2 mm.) into the left renal pelvis.

Dec. 8, 1919. A laparotomy is performed under ether. The left ureter appears normal in shape and circumference. Unusually vigorous peristaltic waves are seen travelling down the left ureter, about two per minute. A bead is visible in the lumen of the ureter about one-third of the way from the renal pelvis to the bladder. The bead does not interfere with the passage of the peristaltic waves, nor is the ureter dilated above it. On opening the renal pelvis only one bead is found remaining there. The mucosa and musculature of the pelvis and ureter appear normal. None of the beads which have been passed are found in the bladder.

DOG 8.—Male. Dec. 16, 1919. Left lumbar incision. Introduction of 8 perforated glass beads into the left renal pelvis. The mean diameter of the beads is 0.085 inch (slightly less than 2 mm.).

Dec. 23, 1919. A laparotomy is performed under ether. The left ureter is hypertrophied in its entire length and the lumen is slightly dilated. Normal peristaltic waves are observed passing down the ureter at regular intervals. No beads are found in the lumen of the ureter and on opening the kidney none are located in the renal pelvis. The uretero-vesical orifice appears to be functioning normally. The right ureter shows nothing unusual.

DOG 9.—Female. Dec. 29, 1919. Left lumbar incision. Introduction of six perforated glass beads into the left kidney pelvis. The mean diameter of these beads is 0.1 inch (approximately 3 mm.).

JAN. 8, 1920. A laparotomy is performed under ether anesthesia. The lower part of the ureter is not dilated or hypertrophied and normal peristaltic waves traverse it at regular intervals. A bead is discovered in the lumen of the ureter about 2 cm. below the renal pelvis. The ureter above the bead is slightly dilated. The bead does not interfere with the passage of the peristaltic waves. On opening the kidney three beads are found free in the tips of the calyces. One other bead is found in the bladder.

DOG 10.—Male. Jan. 2, 1920. Left lumbar incision. Introduction of eight perforated glass beads into the left kidney pelvis. The mean diameter of these beads is 0.1 inch (approximately 3 mm.).

JAN. 15, 1920. A laparotomy is performed under ether. The left ureter exhibits regular vigorous peristaltic contractions. No beads are discovered in the ureter or renal pelvis.

Dog 11.—Male. Jan. 6, 1920. Left lumbar incision. Introduction of five perforated glass beads into the pelvis. The mean diameter of these beads is 0.16 inch (approximately 4 mm.).

Jan. 13, 1920. A laparotomy is performed under ether anesthesia. Two beads are observed in the left ureter about one-third of the way between the renal pelvis and the bladder. These beads appear partially to occlude the ureter because there is a marked degree of hydronephrosis. Strong peristaltic waves, at regular intervals, are observed commencing just below the lowest bead and sweeping down to the bladder. The ureter above the beads exhibits feeble peristalsis. Part of the fluid distending the ureter is aspirated but even then the peristaltic contractions do not become stronger. The waves commence at the renal pelvis but stop at the first bead. Peristalsis below is independent of that above the beads. The opposite ureter behaves normally.

Dog 13.—Male. Jan. 9, 1920. Left lumbar incision. Introduction of seven beads into the left renal pelvis. These beads vary in size within limits of 0.20 to 0.25 inch (5-6 mm.).

Feb. 10, 1920. A laparotomy is performed under ether anesthesia. The left ureter appears slightly dilated and its musculature somewhat thickened. Three beads are found lodged in the lumen of the ureter. The lowermost of them is lodged in the intramural portion. The ureter appears uniformly dilated from this point upwards. About 4 cm. above the first bead a second smaller one is located and about equidistant above this one a third and somewhat larger one. Vigorous peristaltic waves are observed starting at the renal pelvis and descending the ureter to the first obstruction, where they cease. New peristaltic waves are seen to arise immediately below the uppermost bead and proceed toward the bladder. These waves are not interrupted in their course by the second somewhat smaller bead which is rocked to and fro as the contractions sweep by it. No spontaneous antiperistaltic movements of the ureter are observed arising in the neighborhood of any of the beads. On gently pinching the ureter, however, above a bead an antiperistaltic wave is readily elicited. The remaining beads are found in the calyces of the renal pelvis. The mucosa of the pelvis and ureter appears normal. The opposite ureter behaves normally.

#### SUMMARY

The behavior of perforated beads may be summarized as follows:

Beads of small caliber are propelled down the dog's ureter without any difficulty by a series of peristaltic waves and are finally expelled into the bladder. They leave no trace of their former presence in the ureter. Beads of somewhat larger diameter require a longer period to traverse the ureter. They stimulate the ureteral musculature to prolonged peristaltic exertion before they are expelled. Neither a bead of this nor the preceding size obstructs the passage of peristaltic waves from pelvis to bladder. As a result of the passage of several such beads the ureteral wall may become slightly hypertrophied.

Finally beads have been employed which become lodged in the lumen of the ureter, most commonly near the renal pelvis or in the intramural segment. These cause moderate dilatation and hypertrophy of the ureteral wall above the point of obstruction. Vigorous peristaltic waves come down the hypertrophied ureter from the renal pelvis but invariably stop at the bead. Below the bead other peristaltic waves originate and proceed toward the bladder. Antiperistaltic waves have

not been observed arising spontaneously at the point of obstruction although they may be readily called forth by gently pinching the ureter just above the bead.

#### 3. THE BEHAVIOR OF THE URETER DURING REGURGITATION OF FLUID FROM THE BLADDER

Semblinoff,<sup>8</sup> in 1883, and Lewin and Goldschmidt,<sup>9</sup> in 1893, observed that when they injected a colored solution under moderate pressure into the bladder of an anesthetized rabbit the bladder contents regurgitated in many instances into one or both ureters. The latter investigators made the observation that the bladder wall must possess a good degree of tone and be only moderately distended for the experiment to succeed. They also noted that the phenomenon rarely occurred unless peristalsis was visible in the ureters and in many instances they claim to have observed an antiperistaltic wave in the ureter at the moment that regurgitation took place.

Courtade and Guyon<sup>10</sup> repeated Lewin and Goldschmidt's experiments. They were able to produce regurgitation in 20 out of 32 rabbits but in only 5 out of 25 dogs.

Marcus<sup>11</sup> succeeded repeatedly in producing regurgitation in rabbits. He believes that a reversed peristaltic wave is nearly always responsible for the reflux.

On the other hand, Sampson<sup>12</sup> in a series of nearly 20 dogs was unable to produce a reflux of fluid from the bladder into the normal ureter.

Young<sup>13</sup> states that in two cadavers he was unable to force fluid into the ureters by hydraulic pressure. Satani<sup>14</sup> reports that regurgitation of fluid never occurs in the excised bladder and ureter of the pig. He concludes from his experiments that the prevention of a reflux from the bladder into the ureter is complete under normal conditions.

Kretschmer<sup>15</sup> claims to have observed by the use of radiograms on the human subject that solutions of thorium, colargol or cargentos occasionally find their way from the bladder into the renal pelvis by regurgitation. He ascribes both this phenomenon and the so-called retrograde movement of some renal calculi to antiperistaltic contractions of the ureter. Hagner<sup>16</sup> has observed regurgitation of bladder contents into the renal pelvis in two individuals during cystoscopy while the ureteral catheters were *in situ*.

We have repeated Lewin and Goldschmidt's experiments with the main idea of observing the movements of the ureter should regurgitation be found to occur. We have succeeded in duplicating the phenomenon they observed in 10 out of 14 rabbits and also in 1 out of 3 attempts on dogs. The following protocol illustrates the phenomenon as it was observed by us in the rabbit:

RABBIT 1.—Male. Oct. 7, 1919. Ether anesthesia. A number 7F rubber catheter is inserted into the bladder, the bladder emptied and the urethra tied off with the catheter still *in situ*. A laparotomy is next performed and the ureters are exposed under warm, physiological salt solution. Peristaltic waves can be observed traveling at regular intervals down the ureters, averaging one to two per minute with a speed of approximately 30 to

40 mm. per second. This is watched for some minutes. A syringe containing 20 c.c. is meanwhile filled with warm saline stained with methylene blue. The syringe is attached to the catheter and the methylene-blue solution is gradually injected into the bladder so that it becomes moderately distended. While the ureters are under observation a column of blue fluid suddenly fills the lumen of the right ureter. A peristaltic wave which has already left the renal pelvis meets the ascending column in the upper half of the ureter and impedes its progress. Fresh peristaltic waves commence above, becoming more frequent and vigorous and a struggle ensues for control of the ureter. The column of fluid advances towards the kidney and recedes again with each peristaltic wave. Gradually the peristaltic waves completely expel the methylene-blue solution from the ureter and the uretero-vesical orifice closes. The peristaltic waves quickly subside and resume their former frequency of one to two per minute. This phenomenon repeats itself in a few minutes on the same side and also in the left ureter.

Occasionally the ureters are unable to expel the invading fluid. The following instance illustrates this occurrence:

RABBIT 4.—Male. Nov. 10, 1919. After the initial procedures as described in the preceding experiment have been carried out a column of blue fluid is suddenly seen entering the right ureter. Vigorous peristaltic waves attempt to expel the fluid in the ureter, but after a few minutes it is observed that the ureter is becoming more and more distended with methylene-blue solution while the ureteral contractions are becoming feebler and feebler. Finally, the ureteral movements cease entirely and the invading fluid takes complete possession of the ureter and renal pelvis.

The following experiment is cited as an illustration of the rôle played by peristalsis in regurgitation:

RABBIT 15.—Male. Nov. 13, 1919. Ether anaesthesia. The bladder is emptied and a catheter tied into the urethra as usual. A laparotomy is performed. The ureters are quiescent, no peristaltic waves occur while the ureters are watched for several minutes. Methylen-blue solution injected into the bladder fails to enter either ureter. After removal of the solution from the bladder and reinjection of it several times without any success, 0.5 c.c. of a 1 per cent solution of barium chloride is given intravenously. The musculature of the ureters respond to barium chloride by increased peristalsis and in this instance vigorous peristaltic waves are observed in the ureters immediately after injection. As the first peristaltic waves reach the bladder a column of blue fluid ascends each ureter with great suddenness. The peristaltic waves increase rapidly in strength and frequency and the methylene-blue solution is gradually expelled from the ureters and the uretero-vesical sphincter closed.

The following protocol illustrates the occurrence of the reflux in a dog:

Dog 1.—Female. Nov. 19, 1919. Ether anaesthesia. A number 9F rubber catheter is inserted into the bladder, the latter is emptied and the neck of the bladder tied off with the catheter *in situ*. A laparotomy is performed. Both ureters appear normal and are contracting slowly, twice per minute. A syringe is now attached to the catheter and 30 c.c. of warm methylene-blue solution are injected into the bladder. The last cubic centimeter of fluid has hardly been injected before both right and left ureters and renal pelvis suddenly fill with methylene-blue solution. The ureters respond immediately with peristaltic waves of increased frequency and vigor. The methylene-blue solution is completely expelled one or more times from the ureters but immediately reenters them. Finally, the ureters are partially transected midway between

kidney and bladder and the methylene-blue solution is observed to flow from them in spurts interrupted by peristaltic contractions.

Regurgitation was observed in the following rabbit on which a complete ligation of the ureter had previously been done:

RABBIT 13.—Female. Nov. 3, 1919. Complete ligation of the left ureter midway between the kidney and bladder.

Nov. 10, 1919. Ether anaesthesia. A catheter is tied into the bladder. A laparotomy is performed. The left ureter is dilated above the ligature and shows no peristalsis. Normal contractions are seen in the portion of the ureter below the tie and on the opposite side. A syringe is attached to the catheter and 12 c.c. of methylene-blue solution are injected into the bladder. Suddenly after a few seconds' interval fluid enters each ureter, on the right side passing up into the renal pelvis, on the left passing up to the level of the ligature. Vigorous peristalsis is initiated in both ureters and continues uninterruptedly without, however, completely expelling the fluid.

A crystal of barium chloride placed on the wall of the right ureter 5 cm. above the bladder produces a characteristic constriction ring from which contraction waves proceed in both directions. As a result, the methylene-blue solution above the constriction becomes imprisoned and is conveyed back and forth in the ureter by a series of peristaltic and antiperistaltic waves. After the barium chloride has been washed off, it takes nearly ten minutes before peristaltic waves originating in the renal pelvis succeed in passing the point where the barium chloride had caused a constriction.

#### SUMMARY

When a moderate retention is produced in a rabbit's bladder possessing good muscle tone, the uretero-vesical sphincter is occasionally prevented from closing, as it normally does after each gush of urine from the ureter, and the intravesical pressure projects a column of fluid into the ureters. In an animal with quiescent ureters this reflux is difficult to produce. When, however, ureteral peristalsis is stimulated by the injection of barium chloride the bladder content is nearly always regurgitated if there is present a moderate degree of intravesical pressure.

Lewin and Goldschmidt<sup>8</sup> and Marcus<sup>11</sup> believe that antiperistalsis is in many instances responsible for the reflux. In these experiments an antiperistaltic wave preceding the ascending fluid column has not been observed and it is doubted whether reversed peristalsis is ever the cause. The column ascends in our experience at a speed of from 70 to 100 mm. per second, whereas antiperistaltic waves proceeding from a constriction ring in the ureter produced by barium chloride never exceed 40 mm. per second. Furthermore, an observation by Sampson<sup>12</sup> supports our view. He noted that when a cannula was inserted into the uretero-vesical orifice and salt solution passed through the ureter, the ureter responded not by antiperistaltic but by peristaltic waves.

Courtade and Guyon<sup>10</sup> have reported that regurgitation occurs relatively infrequently in dogs, and Sampson<sup>13</sup> was unable to produce it in them at all. From these results Sampson<sup>13</sup> and Young<sup>14</sup> doubt the wisdom of assuming that a comparable phenomenon ever occurs or is even likely to occur in man.

On the other hand, Kretschmer<sup>14</sup> and Hagner<sup>15</sup> have observed regurgitation of fluid from the normal bladder into the ureter during cystoscopy. The former observer believes that the phenomenon noted in man is essentially like that produced experimentally in animals.

It must be emphasized that observations upon cadavers and excised organs are practically valueless in deciding the question of regurgitation. The bladder and ureters in that condition lack tone and peristalsis which, as has been shown, are essential for regurgitation to occur.

All that can be said at present is that regurgitation can be readily produced in the rabbit and somewhat less frequently in the dog. Further observations are necessary before one will be able to say whether a comparable phenomenon occurs in man. Should it occur, it might well be the cause of an ascending infection. It is of course obvious that a reflux of urine may occur in man when the uretero-vesical orifices are pathologically altered.

Far more scepticism, we believe, should prevail concerning the possibility of the conveyance of organisms up the ureter and the retrograde movements of ureteral calculi by antiperistaltic contractions. We have not observed antiperistaltic waves in the rabbit's ureter in which regurgitation was produced, nor have we observed antiperistaltic waves in those animals in which solid bodies have been introduced into the ureters. The burden of proof still rests with those who attempt to explain ascending infection, so-called retrograde movements of some ureteral stones, or ureteral colic, by antiperistaltic movements of the ureter.

#### 4. THE BEHAVIOR OF THE URETER DURING CATHETERIZATION

We have observed the behavior of the ureter in four normal dogs in which a catheter was inserted through the ureteral orifice. The results were quite uniform.

Ether anaesthesia was used. A catheter was introduced through the uretero-vesical orifice and pushed up the ureter for a distance of from 4 to 8 cm. Normal peristaltic waves were observed passing down the ureter at regular intervals. The majority of them on reaching the tip of the catheter appeared to subside and fail to reach the bladder. Reversed peristaltic waves were never observed originating in the wall of the ureter at the tip of the catheter. On several occasions the tip of the catheter was purposely twisted and moved vigorously upwards and downwards, but even then no abnormal movements of the ureter could be elicited.

Finally, Locke's solution and also sodium bromide were allowed to enter the ureter by gravity through the catheter. The response of the ureter to this procedure was the same in all four dogs. The peristaltic waves travelling down the ureter immediately became stronger and more vigorous. If the injection was stopped, the fluid was gradually expelled and peristaltic activity subsided. If on the other hand the injection pressure was increased, the ureter became distended and peristalsis ceased entirely. Reversed peristaltic movements were

never observed during these injections. These observations are similar to Sampson's<sup>16</sup> in which he observed that when fluid was injected into the ureter through a cannula tied into the uretero-vesical meatus, the ureter responded by increased peristaltic waves originating in the renal pelvis and not by reversed peristalsis.

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#### DEVELOPMENT OF POST-GRADUATE INSTRUCTION IN STRASBOURG NEW FRENCH CLINICS

It is interesting to note the beginning of active post-graduate instruction in the newly organized French University of Strasbourg. Professor Pautrier, at the University Clinic for Diseases of the Skin at the Civil Hospital, is giving a post-graduate course in dermatology and venereal diseases, running from May 1 to July 14. The courses consist of 40 clinical exercises and 10 exercises in the laboratory, amounting to five periods a week. Special arrangements are being made for the students which may permit of their carrying on work during free hours. The honorarium for the course is 300 francs. Arrangements may be made directly through Professor Pautrier.

W. S. T.

# THE FATE OF BACTERIA INTRODUCED INTO THE UPPER AIR PASSAGES

## V. THE FRIEGLÄNDER BACILLI

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In previous papers<sup>1</sup> we have reported studies on the fate of various bacteria introduced into the upper air-passages. An attempt has been made to analyze the mechanism involved in the disposal of the organisms and as far as possible to interpret its significance. For reasons discussed below it seemed that a study of the Friedländer bacilli would be of particular interest in this connection, and the present report deals with the fate of these organisms after their introduction into the upper air passages.

### THE FRIEGLÄNDER BACILLI

Although the name of Friedländer was originally coupled with the bacillus which he observed in cases of pneumonia, a number of organisms are now loosely included in a group under the general designation of the Friedländer bacilli. The characteristics of these organisms may be briefly summarized as follows: Morphologically they appear as short bacilli, often coccoid in form, non-motile and non-spore forming. They are usually surrounded by a well defined capsule which may disappear when they are grown outside the body. The organisms are decolorized when stained by Gram's method. From the point of view of artificial cultivation they may be spoken of as hardy, since they thrive within wide limits of temperature on all the ordinary media. The growth is characteristic, consisting of huge greyish white sticky colonies which tend to become confluent. They may reach a diameter of a centimeter. Various attempts have been made to group these organisms on the basis of sugar fermentation or immunity reactions, but inasmuch as the strains are subject to minor variations no satisfactory classification has been attained. Coulter,<sup>2</sup> however, was able to show that eleven non-lactose fermenting strains derived from various sources represented a single biological group when tested by their reaction to artificial agglutinative sera.

### INCIDENCE OF *B. FRIEGLÄNDER* IN DISEASE

Although this organism is not the common cause of lobar pneumonia as Friedländer originally claimed, it does occasionally produce a severe and almost invariably fatal form of pulmonary infection. Sisson and Thompson<sup>3</sup> in 1915 reported four such cases and reviewed the literature. At that time they were able to find records of only 33 cases of pneumonia undoubtedly due to the Friedländer bacillus. During the past eight years two instances of this condition have been observed in the medical wards of The Johns Hopkins Hospital. It is the most picturesque disease process caused by this organism, almost always ending in septicemia and death. Luetscher<sup>4</sup> encountered the Friedländer bacillus twice in 603 sputum cultures made in 459 cases of non-tuberculous respiratory infection. It may also occasionally be found in infected paranasal sinuses, and in middle ear disease where it seems to play the part of a secondary invader. We have obtained it in almost pure culture from the sputum of a patient with a subacute lung abscess. On the whole, then, this group of bacteria play a negligible part in human pathology with the paradox that, when they do produce disease, it is almost uniformly fatal.

### INCIDENCE OF *B. FRIEGLÄNDER* IN HEALTHY PEOPLE

The organism is said to be an occasional saprophytic inhabitant of the healthy intestine. It is found but rarely in the mouths and upper air passages of healthy people and can in no sense be regarded as a member of the normal mouth flora. On the other hand, when it is present in the throat it can usually be recovered on repeated examinations over long periods of time—a relatively permanent carrier state exists. On examining a series of 46 people we found Friedländer bacilli in the throats of three. In one case 14 of 16 cultures made during a period of three months showed the organisms, and in another case they were present in 13 of 15 cultures during a period of four months. In neither of these men was there a history of any previous respiratory infection, the throats presented no obvious abnormality and, although they both had chronic cardiac decompensation with oedema of the lungs they developed no autogenous pulmonary infection with these organisms. One of these patients remained in the ward for five months. During this period 285 throat cultures were made on 31 other patients in the same ward. No Friedländer bacilli were found in any of these cultures although the patients were in close contact with the carrier.

We may therefore summarize the rather anomalous conduct of this organism as follows: (1) It occurs very uncommonly in normal throats, but (2) when present persists with great tenacity. (3) There seems to be no tendency for contacts to acquire the organism from a carrier. (4) It very rarely produces disease, and never disease in epidemic form, but occasionally may set up a severe and fatal infection.

In view of the above facts it seemed of particular interest to study the fate of this organism when experimentally introduced into the upper air passages.

### METHODS

Three strains were used. Strain A was isolated in almost pure culture from an acute purulent sinusitis. The organism possessed the following characteristics:

TABLE I.—FATE OF *B. FRIEDELANDER* SWABBED ON THE TONGUE

Date	Name	Procedure	Number of colonies of <i>B. Friedländer</i> per plate recovered from tongue and pharynx										Control culture before inoculation	
			Tongue				Pharynx							
			After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 3 days	After 4 days	Tongue	Pharynx
Jan. 12.	S.	One loop of <i>B. Friedländer</i> (Strain A) rubbed on tongue.	∞*	A few cols. F.	No F.	No F.	Many cols. F.	A few cols. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 13.	E. S.	One loop of <i>B. Friedländer</i> (Strain A) rubbed on tongue.	∞	3 cols F.	No F.	No F.	Many cols. F.	1 col. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 14.	G.	One loop of <i>B. Friedländer</i> (Strain A) rubbed on tongue.	∞	50 cols. F.	No F.	No F.	100 cols. F.	1 col. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 15.	L.	One loop of <i>B. Friedländer</i> (Strain G) rubbed on tongue.	∞	30 cols. F.	No F.	No F.	500 cols. F.	200 cols. F.	No F.	No F.	.....	.....	No F.	No F.
Mar. 27.	J.	One loop of <i>B. Friedländer</i> (Strain B) rubbed on tongue.	∞	50 cols. F.	No F.	No F.	∞	20 cols. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 18.	Hd.	One loop of <i>B. Friedländer</i> (Strain R) rubbed on tongue.	∞	∞	No F.	No F.	∞	∞	No F.	No F.	.....	.....	No F.	No F.
Jan. 13.	St.	One loop of <i>B. Friedländer</i> (Strain G) rubbed on tongue.	∞	Many cols. F.	A few cols. F.	No F.	∞	Several hundred cols. F.	100 cols. F.	200† cols. F.	No F.	No F.	No F.	No F.
April 5.	T.	One loop of <i>B. Friedländer</i> (Strain G) rubbed on tongue.	∞	∞	1 col. F.	No F.	∞	∞	No F.	No F.	.....	.....	No F.	No F.
Mar. 28.	G.	One loop of <i>B. Friedländer</i> (Strain R) rubbed on tongue.	∞	No F.	No F.	No F.	∞	No F.	No F.	No F.	.....	.....	No F.	No F.

\* ∞ = Innumerable.

† Throat a little red. No symptoms.

TABLE II.—FATE OF *B. FRIEDELANDER* SWABBED ON THE NASAL SEPTUM

Date	Name	Procedure	Number of colonies per plate of <i>B. Friedländer</i> recovered from nose and pharynx								Control culture before inoculation	
			Nose				Pharynx					
			After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 10 min.	After 2 hours	After 24 hours	After 48 hours	Nose	Pharynx
Mar. 10.	H.	One loop of <i>B. Friedländer</i> (Strain G) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	No F.	No F.	No F.	No F.	No F.
Mar. 8.	C.	One loop of <i>B. Friedländer</i> (Strain G) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	10 cols. F.	No F.	No F.	No F.	No F.
Mar. 6.	Co.	One loop of <i>B. Friedländer</i> (Strain R) swabbed on left nasal septum.	∞	30 cols. F.	No F.	No F.	No F.	No F.	No F.	No F.	No F.	No F.
Mar. 8.	J.	One loop of <i>B. Friedländer</i> (Strain R) swabbed on left nasal septum.	∞	1000 cols. F.	2 cols. F.	No F.	No F.	Many cols. F.	No F.	No F.	No F.	No F.
Jan. 14.	W.	One loop of <i>B. Friedländer</i> (Strain A) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	A few cols. F.	No F.	No F.	No F.	No F.
April 4.	G.	One loop of <i>B. Friedländer</i> (Strain G) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	Many cols. F.	No F.	No F.	No F.	No F.

TABLE III.—FATE OF *B. FRIEDELANDER* INTRODUCED INTO TONSIL CRYPTS

Date	Name	Procedure	Number of colonies per plate of <i>B. Friedländer</i> recovered from crypt and pharynx								Control culture before inoculation			
			Crypt				Pharynx							
			After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 3 days	After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 3 days	Crypt	Pharynx
Mar. 6.	J.	One loop of <i>B. Friedländer</i> (Strain A) placed in a tonsil crypt.	∞	∞	500 cols. F.	No F.	.....	Several hundred cols. F.	100 cols. F.	1 col. F.	No F.	.....	No F.	No F.
Mar. 8.	S.	One loop of <i>B. Friedländer</i> (Strain G) placed in a tonsil crypt.	∞	∞	No F.	No F.	.....	∞	Several hundred cols. F.	No F.	No F.	.....	No F.	No F.
Mar. 10.	U.	One loop of <i>B. Friedländer</i> (Strain R) placed in a tonsil crypt.	∞	Several hundred cols. F.	100 cols. F.	A few cols. F.	No F.	10 cols. F.	200 cols. F.	No F.	No F.	No F.	No F.	No F.

Growth: Large, confluent, opalescent, very viscid stringy colonies.

Morphology: Typical small Gram-negative bacilli. Marked capsule formation.

#### Sugar Fermentation (24 hours):

	Acid	Gas
Dextrose .....	+	+
Saccharose .....	0	0
Lactose .....	0	0
Mannite .....	+	+

The first inoculation was made from a subculture on blood agar of the original culture, and thereafter freshly recovered organisms from the experimental inoculations were used. Alteration by artificial growth was therefore reduced to a minimum.

*Strain R* was recovered practically in pure culture from the sputum of a patient with a lung abscess. Its characteristics were as follows:

Growth: Moderately large (0.5 cm.), confluent, opalescent, very viscid stringy colonies.

Morphology: Typical small Gram-negative bacilli. Marked capsule formation.

#### Sugar fermentation (24 hours):

	Acid	Gas
Dextrose .....	+	+
Saccharose .....	0	0
Lactose .....	0	0
Mannite .....	+	+

*Strain G* was obtained from a healthy carrier who showed no striking abnormality of the upper air passages. The organism was freshly isolated before each inoculation. Its characteristics were as follows:

Growth: Very large (up to 1 cm.), confluent, greyish white, viscid, slightly stringy colonies.

Morphology: Typical small Gram-negative bacilli. Well marked capsule formation.

#### Sugar fermentation (24 hours):

	Acid	Gas
Dextrose .....	+	+
Saccharose .....	+	+
Lactose .....	Very slight.	Very slight.
Mannite .....	+	+

These three strains, therefore, included organisms from acute and chronic disease processes, as well as those which were apparently leading a harmless parasitic existence in a carrier.

The methods were the same as those employed in the previous work.<sup>1</sup> Solid masses of a 24-hour growth were swabbed upon the tongue, nasal septum, and in the tonsil crypts of healthy individuals with clinically normal upper air passages, and cultures were made at various intervals on bile agar plates.

#### EXPERIMENTS

**EXPERIMENT I.**—*B. Friedländer* was swabbed on the tongue, and cultures were made from the tongue and pharynx after 10 minutes, 2 hours, 24 hours, and 48 hours. The results are summarized in Table I.

**Summary.**—*B. Friedländer* swabbed on the tongue was rapidly spread over the whole mouth cavity. The organisms disappeared with remarkable rapidity. After two hours cultures from the tongue and pharynx in five of nine cases showed only a few colonies. After 24 hours no *Friedländer* bacilli were recovered from the pharynx in eight of the nine cases. In one instance they persisted for two days and then were recovered no more.

**EXPERIMENT II.**—*B. Friedländer* was swabbed on the mucosa of the nasal septum and cultures were made from the nose and from the pharynx after 10 minutes, 2 hours, 24 hours, and 48 hours. The results are summarized in Table II.

**Summary.**—*B. Friedländer* swabbed on the nasal septum could not be recovered from the nose after 24 hours in five out of six cases. In one instance two colonies were obtained after 24 hours, but none after 48 hours. The organisms were carried rapidly to the pharynx from which they were recovered in variable numbers up to 24 hours.

**EXPERIMENT III.**—*B. Friedländer* was introduced into tonsil crypts and cultures were made at various intervals for several days from the crypts and from the pharynx. The results are summarized in Table III.

**Summary.**—*Friedländer* bacilli deposited in tonsil crypts disappeared rapidly, although they persisted a little longer than when swabbed on the free surface of the mucous membranes. This was probably due to mechanical retention, as there was no evidence of any lesion and the organisms were eliminated in from one to two days.

In summary, then, *B. Friedländer* experimentally introduced into the upper air passages in various ways disappeared rapidly—usually in less than 24 hours. There was no tendency to the production of a carrier state and no disease was set up.

#### THE MECHANISM OF THE DISPOSAL OF *B. FRIEDLÄNDER*

In the previous studies on the fate of organisms placed in the upper air passages, we attempted an analysis of the factors involved in effecting their rapid disposal. It became apparent that, as a rule, the mechanical flushing action of the secretions was the most important means of eliminating foreign organisms, and this principle seems to apply to the *Friedländer* bacilli as well. The effect of saliva on the growth of these organisms was studied *in vitro*. They survived and multiplied for days in salivas of various reactions, readily overgrowing the ordinary mouth bacteria. An illustrative protocol is shown in Table IV.

TABLE IV.—EFFECT OF SALIVA ON THE GROWTH OF  
*B. FRIEDLÄNDER*

Time of culture (one loop of mixture from each tube plated)	Tube 1. 0.5 cc. saliva	Tube 2. 0.5 cc. salt sol. + 1 loop <i>B. Friedländer</i>	Tube 3. 0.5 cc. saliva + 1 loop <i>B. Friedländer</i>
Immediately .....	Mouth flora.....	∞ Friedländer .....	∞ Friedländer + mouth bacteria.
After 4 hours (37°).	Mouth flora.....	∞ Friedländer (but fewer).	∞ Friedländer + mouth bacteria.
After 1 day (37°)...	Mouth flora.....	∞ Friedländer (but fewer).	∞ Friedländer + mouth bacteria.
After 2 days (37°)..	Mouth flora.....	60 cols. Friedländer.	∞ Friedländer + fewer mouth bacteria than in previous cul- ture.

## DISCUSSION

In previous experiments it was shown that various organisms—*Sarcina lutea*, *B. coli*, *Staph. albus*, and *B. influenzae*—introduced into the upper air passages of normal individuals disappeared with great rapidity—usually within 24 hours. This rate of elimination was found to correspond with the speed of disappearance of inert particles, and a longer persistence in occasional cases was explained on a mechanical basis. It seemed that the normal intact mucous membranes offered no opportunity for colonization or invasion by these organisms, but that they were impervious much as the normal intact skin surfaces are. To the above list of bacteria *B. Friedländer* may now be added. It appears that a variety of strains freshly isolated both from disease processes and from the throat of a healthy carrier disappear at the usual rate of speed—usually within 24 hours.

These facts, which are quite in harmony with the observations on contacts mentioned above, do not explain the mechanism of the chronic carriers found among normal people, nor the occasional cases of severe infection due to this group of organisms. They bring strong support, however, to the impression

gained from epidemiological study that the rôle of the Friedländer bacillus in disease is essentially one of a secondary invader, and that when it produces disease which is apparently primary, a very special set of favoring circumstances must be present.

## CONCLUSIONS

1. Friedländer bacilli freshly isolated from various sources were introduced into the normal upper air passages without producing local or general disease.
2. The organisms disappeared rapidly—usually within 24 hours.
3. It was not possible artificially to produce a carrier state.
4. The bacteria are removed by mechanical means.
5. This group of organisms when associated with disease usually act as secondary invaders.

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## A PHYSIOLOGICAL STUDY OF THE EUSTACHIAN TUBE AND ITS RELATED MUSCLES

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The tympanic membrane functions perfectly only when the atmospheric pressure is the same on both sides of it. The tension resulting from an inequality in pressure may cause severe pain from the bulging and stretching of the membrane, may even be sufficient to rupture it, and in all cases impairs its vibratory function until the pressure equilibrium is again restored. This equalization of pressure is made possible by the inflow of atmospheric air from the nasopharynx through the Eustachian tube into the tympanic cavity until the tension of the air within this cavity becomes identical with that of the air in the external auditory canal. It is a matter of common knowledge that sudden changes in atmospheric pressure may so affect the ear-drum that its proper functioning is disturbed, and the exposure of aeronauts to such conditions is, of course, a matter of history. During the late war, however, interest was more forcibly attracted to this subject, since aviators in the service, while making sudden changes in altitude, often suffered distressing difficulties referable to the ear-drum. This study was begun, at the suggestion of Dr. W. H. Howell, in the effort to learn something of that part of the physiology of the Eustachian tube which is concerned with its action as a protective mechanism of the ear-drum. It was believed that, perhaps, a clear understanding of this mechanism might disclose some simple associated movement through which an opening of the Eustachian tubes could, when necessary, be effected quickly at will. At the outset, however, it must be confessed that these experiments have

led to no new or peculiarly efficient voluntary method of dilating the tubes. The physiological mechanism of the Eustachian tube was found to be linked with certain reflexes described below, and the study of this mechanism has led to the belief that those who state that they are able quickly and efficiently to open their Eustachian tubes by protrusion of the lower jaw and other similar movements are more probably erroneously interpreting various synchronous but dissociable aural sensations (such, for instance, as the rumble produced by the contraction of the *tensor tympani*) as a dilatation of the tubes. Nevertheless, on the physiological side, a certain amount of information has been acquired during this study, which, it is hoped, may serve to lessen somewhat the confusion and uncertainty which pervades the literature concerning three points of fundamental importance in any consideration of the physiology of the Eustachian tube: (1) The physiological conditions under which the tube is open; (2) the muscles which influence the patency of the tube; (3) the innervation of those muscles. The present paper is concerned only with the first two of these questions. Experiments bearing upon the nerve supply of the palatal muscles in the region of the Eustachian tube will appear in a separate report.

### I. THE PHYSIOLOGICAL CONDITIONS UNDER WHICH THE TUBE IS OPEN

Eustachius, in the sixteenth century, described the tube connecting the tympanic cavity with the nasopharynx. He believed that this tube normally was open; and up to 1853

the two cavities were generally considered to be always continuous, this condition being supposed to be necessary for perfect hearing. It was Toynbee,<sup>3</sup> in 1853, who first definitely insisted that the pharyngeal orifice of the tube normally is closed, and that it is opened during deglutition to permit an inflow of air. He arrived at this conclusion especially from a consideration of his now well-known experiment of swallowing with both mouth and nose closed, which causes a feeling of tension of the tympanic membranes because of the disturbed air-pressure within the Eustachian tubes. If now the mouth and nose be opened, a return to the normal pressure-balance should occur immediately if the pharyngeal orifices of the tubes be always open. No such change occurs, however, until a second swallowing movement is performed with the nose open; but this is invariably accompanied by a relief of the pressure sensations, indicating that the tubes have opened during the act to admit atmospheric air from the nasopharynx.\* Toynbee noted, further, the practice of swallowing to relieve the inequality of pressure on the two sides of the ear-drum which occurs during descent in a diving bell, as the pressure in the external auditory canal continually increases.

In 1861 Politzer<sup>5</sup> devised a little manometer to be fitted into the external auditory canal, which, he claimed, would indicate pressure changes within the Eustachian tube because of the consequent displacement of the tympanic membrane. From a rise of the fluid level during swallowing he concluded that the tube opens during the reflex to admit an inflow of air. Jago,<sup>6</sup> however, after repeating these experiments, wrote that Politzer's manometer is subject to too many sources of error to be productive of any reliable information. On the anatomical side, Von Tröltzsch<sup>7</sup> shortly afterward deduced from a careful study of the relations of the muscles of the region that normally the tube is closed but must open during deglutition.

With the invention of the rhinoscope and nasopharyngoscope a more direct method of observing the pharyngeal orifice of the tube became available; and Cutter,<sup>8</sup> from his rhinoscopic studies in 1867, states most positively that normally the tubal orifice is open but that it closes during swallowing. Cleland<sup>9</sup> came to the same conclusion as a result of his own observations in 1868; and indeed Cutter's continued studies<sup>10</sup> led him in 1872 to the conclusion that "the Eustachian tubes are open at all times" during the swallowing reflex as well as while at rest. In 1873 Rumbold<sup>11</sup> records the opposite conclusion from his experiments and clinical observations that "during the act of deglutition the Eustachian tube is not an open passage into the tympanum," but that the tubal walls are always in slight contact. General opinion at that date, however, seemed to lean toward the view of Politzer and Von Tröltzsch—that the tube is closed when at rest and opened

during deglutition; but it was an opinion unverified and further conflicting experiments and observations served to intensify the uncertainty. Thus, in 1880, Fournié<sup>12, 13</sup> described his experiments on the Eustachian tube and wrote:

"Contrairement à l'opinion généralement adoptée de nos jours, la trompe d'Eustache est toujours ouverte, et la communication de l'air extérieur avec celui de la cavité du tympan est incessante. L'obturation de la trompe n'est jamais que momentanée et elle se produit jour et nuit pendant les mouvements de deglutition, pendant la prononciation de certaines lettres, pendant le chant."

Semeleider,<sup>14</sup> from rhinoscopic observations, described a narrowing of the pharyngeal orifice accompanying every elevation of the soft palate; and Lucae<sup>15</sup> concluded from his studies on human subjects that "with vigorous elevation of the soft palate, also during swallowing and phonation, there occurs a closure of the mouth of the tube" which "is again opened when the soft palate descends." In another study of the Eustachian tube Lucae<sup>16</sup> records his observations which led him to believe that the tubal orifice opens during expiration and closes during inspiration: "Bei sehr tiefer Inspiration fand sojar ein volliger Verschluss der Tubamundung stat, während dieselbe bei expiration deutlich klappte"; and in 1903 Patel,<sup>17</sup> observing directly the tubal orifices in a patient who had suffered a neoplastic erosion of the flesh and bone on one side of the face, described vague movements of opening and closing of the tubal orifices during respiration.

From their respective experiments, Dionisio<sup>18</sup> in 1912, and Bilancioni<sup>19</sup> in 1914, arrived at the conclusion that the tube is normally closed, and opens during swallowing; whereas Caldera<sup>20</sup> in 1915 wrote in refutation of their work that one cannot limit the opening of the tube to the periods of deglutition, his observations apparently demonstrating that the Eustachian tubes, under normal conditions, are always open.

Among present-day texts we find Piersol<sup>21</sup> stating that the tube is normally closed, but is opened during deglutition, mouth-breathing, and whenever the palate is raised. Cunningham<sup>22</sup> is more non-committal: "During the act of swallowing it is generally thought that the auditory tube is opened by contraction of the tensor veli palatini muscle which arises from it. It has been held, on the other hand, that the auditory tube is closed during swallowing by compression of its wall by the contraction of the levator veli palatini."

#### EXPERIMENTS\*

Politzer<sup>5</sup> has pointed out that the muscular relations of the Eustachian tube of the dog correspond closely with those of man. This close similarity of regional anatomy was confirmed during the present work by comparisons of dissections of embalmed human subjects and formalin specimens of dogs' heads; and further by comparisons of dissections of the region, made upon the unembalmed bodies of human subjects at the autopsy table, with the dissections made upon anesthetized dogs during these experiments. Dogs, therefore, were used in all of the animal experiments described in this paper.

The exposure of the pharyngeal orifices of the Eustachian tubes can be carried out in the following manner: A dog is

\* It is interesting to note that although this experiment now bears Toynbee's name, Maissiat<sup>23</sup> had written fifteen years previously: "Qu'on se tienne le nez pincé, la bouche étant close, et qu'on fasse effort pour inspirer, l'ouïe est assourdie d'une certaine manière; les narines étant redouvenus libres, avalez quelque chose, votre salive, l'ouïe se rétablit parfaite."

anesthetized, tracheotomy performed and connection established with an ether-respiration apparatus by means of a tracheal cannula. Both common carotid arteries are ligated to minimize hemorrhage, as it is desirable to introduce about the delicate palatal muscles as few ligatures as possible. The immediate collateral circulation is ample to maintain satisfactorily the nutrition of the structures during the experiment. A mouth-gag is introduced to hold the jaws widely separated and the tongue is drawn forward and stitched to the lower lip. The hamular processes of the pterygoid bones can be felt on either side as distinct, bony prominences in the roof of the mouth. Using these as landmarks, an incision is made through the soft palate from a point about one centimeter anterior to them, extending backward in the mid-line almost to the insertions of the levatores palati in the uvular region. This incision exposes the nasopharynx, so that the orifices of the Eustachian tubes can be clearly seen, situated on either side just posterior to the hamular processes of the pterygoid bones. In some experiments the fibrous expansion of the tendons of the *tensores palati* (which forms a fascial layer of the soft palate) was exposed intact, in order to study the action of that muscle. In almost all cases, the midline insertions of the levatores palati were left uncut, since a perfect exposure of the tubal orifices may be obtained without their destruction.

The orifices of the Eustachian tubes appear as slits in the mucous membrane of the nasopharynx. The anterior lip of the slit consists of fibrous tissue covered with mucous membrane which extends into the tube. The posterior cartilaginous lip appears as a curved prominence beneath the mucous membrane. The two lips are plainly seen to lie, normally, in contact; *i.e.*, the tubal orifice is normally closed, when at rest.

Deglutition is readily effected by mechanical stimulation of the pharynx. Invariably the swallowing reflex is accompanied by a wide gaping of the tubal orifices. This gaping can be seen to be brought about by the membranous wall being drawn anteriorly away from the cartilaginous wall, the latter undergoing no appreciable change of position, although the mucous membrane about it is somewhat disturbed by the contraction of the underlying levator palati muscle. The opening of the tube is quite sudden and brief, and occurs at the moment of greatest contraction of the upper pharyngeal muscles—when the hyoid bone is at the height of its ascent. Nasopharyngoscopic observations upon normal human subjects also show clearly that there occurs a gasping dilatation of the mouth of the tube during deglutition; and this opening of the tube appears similar in all important respects to the process as observed in the dog.

During the most forced respirations which can be elicited reflexly by the stimulation of sensory nerves, the pharyngeal orifices of the tubes remain closed, even though the palate is being elevated vigorously by the levatores palati, which, by reason of their contractions during forced respiration—a phenomenon which has been invariably observed during these experiments—seem to warrant consideration as accessory

muscles of respiration.\* Their contractions will be synchronous with inspiration or expiration depending upon which of these movements is the “active” and more prominent one during forced respiration. It has been held that “whenever the palate is raised . . . the tensor palati and levator palati contract, and in so doing open the Eustachian tube.”<sup>10</sup> Elevation of the palate, alone, is certainly not accompanied by an opening of the Eustachian tube. It will be shown that the contraction of the tensor palati muscle is the *conditio sine qua non* of every physiological opening of the tube; and simple levation of the palate is by no means invariably accompanied by a simultaneous contraction of the tensor palati—a fact which can be clearly determined by watching directly the naked muscles during forced respiration in a preparation such as will be described below; the levator will be seen to execute definite respiratory contractions, while the tensor remains perfectly at rest and the tube remains closed.

A study of the pharyngeal orifices of the Eustachian tubes in human subjects, by means of the nasopharyngoscope, allows one to understand, perhaps, why the literature contains conflicting statements about them; for there are, clearly, individual differences in the appearance of the orifices. Furthermore, there are observed variations in the reactions of the orifices in the same individual at different times, so that during forced respiration or elevation of the palate produced by the enunciation of “Ah” or “U,” there will be seen at one time only a disturbance of the fold of the mucous membrane which overlies the contracting levator palati muscle, the tubal orifice remaining closed, whereas at another time the same individual will exhibit what appears to be an actual opening of the orifice during these movements. But it should be recognized that it is very difficult to draw any very clear-cut conclusions from nasopharyngoscopic observations of slight movements of the mouth of the tube, for the orifice itself lies almost hidden within a funnel-shaped hood, the mucous membrane of which is disturbed by almost every movement of the soft palate, and shadows produced by the movements of this region are perhaps not so easy to interpret as has been assumed. Careful observation of the orifices in human subjects will allow here, then, only the following statements: During quiet respirations the orifices remain closed; during elevation of the palate, whether by forced respiration or by other means, there is usually seen only a disturbance of the mucous membrane, brought about by the contraction of the underlying levator palati muscle; in some instances there has appeared a disturbance of the membrane to such a degree that the orifice appeared somewhat dilated, but in no case did there occur during elevation of the palate the unmistakable wide gaping of the orifice which is so strikingly seen during swallowing. It is not impossible that contraction of the tensor palati may occur synchronously with elevation of the palate at times other than during the swallowing,

\* Debrou<sup>11</sup> noted clinically the elevation of the palate during forced inspiration, and quotes Albinus<sup>12</sup> as having also been aware of this.

yawning and sneezing reflexes; and such elevation of the palate would consequently be accompanied by an opening of the tube. But elevation of the palate without opening of the tube is to be regarded as the rule, for this is clearly true in the dog; and further, if Toynbee's experiment be followed by forced respiration, or by elevation of the palate produced by the enunciation of "Ah" or "U," no equalization of pressure within the tube will occur. In no instance was there seen during elevation of the soft palate the narrowing of the orifice which has been described and assumed to occur as a theoretical effect of the contraction of the levator palati muscle. On the contrary, the palate is vigorously elevated during deglutition and it is during this act that the orifices are most widely gaping.

It has been held<sup>19</sup> that the tube is opened by mouth breathing; and it has been suggested that the virtue of the unconscious opening of the mouth in attentive listening may be associated with the patency of the tube accompanying such a position. The present experiments, however, were all made upon animals breathing with wide-open mouths, and the tubal orifices were clearly seen to be closed. Nasopharyngoscopic observations made upon human subjects also showed that there occurs no dilatation of the ostium during mouth-breathing; nor was there seen any change in the condition of the orifice in subjects who were requested to listen concentratedly, with the mouth open, for the ticking of a watch which was gradually brought within the range of hearing. And indeed, if the experiment of swallowing with the mouth and nose closed be followed by mouth-breathing with attentive listening, no restoration of pressure balance will result. Hence we must conclude that the Eustachian tube is not opened during this maneuver. It has long been believed that "concussion of the tympanic membrane from loud reports is minimized by mouth-breathing,"<sup>20</sup> and the reason assigned has been the supposed accompanying opening of the tube. It is not improbable that mouth-breathing merely offers a larger portal of entry into the nasopharynx for the concussion waves which may force themselves into the Eustachian tubes after the manner of air in the Valsalvian experiment; and in such a way there will be exerted an equal pressure effect upon both sides of the tympanic membrane; but any such effect of mouth-breathing which may exist cannot be ascribed to a consequent patency of the Eustachian tube.

During many hours of observation, the tubal orifices of dogs have never been seen to open independently of the swallowing reflex; they exhibit neither periodic nor irregular independent reflex dilatations. It was thought, however, that perhaps the mere existence of a difference in pressure on the two sides of the tympanic membrane might be a sufficient stimulus to set in motion a reflex opening of the tube and a consequent restoration of pressure-balance. Certainly the pressure inequality brought about by swallowing with the mouth and nose closed is followed by no such reflex equalization of pressure; and it is well known that many persons are at a loss to know what they can do to relieve the pressure

disturbance experienced during transit through the Hudson tubes—a fact which argues against the existence of any reflex adjustment. Further, Green,<sup>21</sup> in a report of his studies on the effects upon the Eustachian tube of descent in a diving-bell, described the actual rupture of the tympanic membrane owing to the inequality of pressure exerted upon it; and he states that this occurred especially in persons un instructed in the method (swallowing) of restoring the pressure-balance on the two sides of the membrane. Indeed, it will be remembered that it was the apparent lack of such a reflex adjustment in the case of aviators which led to the present study. However, in pursuit of the possibility of a reflex adjustment, the atmospheric pressure in both external auditory canals was raised greatly by means of rubber atomizer bulbs, which were sealed into the ears of anesthetized dogs. No opening of the tubes occurred; nor did this pressure disturbance set in motion a swallowing reflex as a means of opening the tubes. Blasts of air were directed against the pharyngeal orifices without effect; nor did mechanical stimuli or increased air pressure within the tubes cause either an independent dilatation or a swallowing reflex. It appears that the swallowing reflex, as a means of equalizing the atmospheric pressure on the two sides of the tympanic membrane is consciously (often habitually), but not reflexly, subservient to the demands of the membrane; and the opening of the tube during deglutition, although a most important function, is, however, merely a by-product of this frequent reflex. Certainly, the existence of an inequality of pressure on the two sides of the tympanic membrane is not, in itself, a stimulus that will set in motion a reflex opening of the tubes and a consequent restoration of pressure equilibrium.

In human subjects the tubal orifices were seen to open reflexly only during deglutition and sneezing.\* Attempts were made during several hours to watch the orifices during the yawning reflex, but the presence of the nasopharyngoscope within the upper respiratory passage inhibited completely the execution of this reflex. However, it is certain that the Eustachian tubes are opened during yawning, for if the middle ears are inflated either by Toynbee's or by Valsalva's experiment (forced expiration with mouth and nose closed) a yawn will bring about a restoration of pressure-equilibrium which is usually even more satisfactory than that attendant upon the swallowing reflex. One derives the distinct sensation that the tubes are held open during the yawning reflex for a longer period of time than during deglutition. It is, therefore, not true that "of all the movements of the muscles of the soft palate, there is none which exercises such an influence in opening the tube as the act of swallowing."<sup>22</sup> The dilatation of the Eustachian tubes must be regarded as a most important function of the yawning reflex, for the tubes are ventilated during this act with a peculiar thoroughness.

\* The opening of the tubal orifice during sneezing was seen during a nasopharyngoscopic examination of a human subject by Dr. E. N. Broyles, to whom the writer is greatly indebted for his interest and assistance which made possible the clinical nasopharyngoscopic observations recorded here.

However, what has been said concerning the relation of the swallowing reflex to the pressure-balance on the tympanic membrane is applicable also to the yawning reflex; for a disturbance of the pressure-balance will not provoke a yawning reflex as a means of restoring equilibrium.

## II. THE MUSCLES WHICH INFLUENCE THE PATENCY OF THE TUBE

Discussing the opening of the Eustachian tube during the act of swallowing, Yule<sup>2</sup> wrote: "Owing to the extreme complication of the act, no observer has yet been able to ascertain which the efficient salpingeal muscles are"; and up to the present time no satisfactory experimental evidence has been brought to bear upon this question.

The tensor palati muscle (tensor veli palatini; spheno-staphylinus; circumflexus palati; external peristaphylin)<sup>\*</sup> and the levator palati muscle (levator veli palatini; salpingo-staphylinus; internal peristaphylin) by reason of their intimate anatomical relations to the Eustachian tube have long been associated with the physiology of this structure. In 1707 Valsalva,<sup>3</sup> after describing the tensor as a "Novus Tubæ Eustachiae Musculus," drew attention to its attachment along the membranous wall of the tube and regarded the muscle as a dilator of this structure. The levator palati he termed the "salpingostaphylinus," because of its close anatomical relation to the tube. About the tensores and levatores palati muscles has centered the greater part of the discussion concerning the movements of the Eustachian tube.

In 1853, Toynbee<sup>4</sup> revived Valsalva's original conception that the tensor palati is a dilator of the Eustachian tube. Politzer<sup>5</sup> was convinced of this; and in 1864 Von Tröltzsch<sup>6</sup> published his careful anatomic studies on the relation of the tensor to the tube. He believed that it must act as a dilator and wrote: "The problem is to prove on anatomical grounds that, during the act of swallowing, the tensor palati has (or gains) a fixed point below, so that the fibers arising from the membranous portion of the tube are able to carry out their activity in this direction." He concludes that during deglutition the soft palate becomes this "fixed point." It will be

\* "The tensor palati arises from the inferior surface of the sphenoid bone and the inner plate of the pterygoid processes; a great number of its fibers also arise from the short, hook-like, lateral cartilaginous wall, and from the membranous part of the tube. In its downward course its flat belly lies close to the lateral wall of the membranous tube and is rather firmly attached to it. The direction of its fibers forms an acute angle with the cartilaginous part of the tube and its tendon, winding around the hamulus pterygoideus, radiates into the fibrous prolongation of the hard palate. The tendon of the muscle is so tightly attached to the hamular process that the effect of its contraction is greater on the Eustachian tube than on the soft palate."

"The levator palati arises from the inferior surface of the petrous bone bordering on the carotid canal. Its rounded belly runs parallel to the Eustachian tube, is closely applied to the membranous portion which forms the floor of the tube and is inserted in a radiating manner into the soft palate below its pharyngeal orifice. None of its fibers arise from the Eustachian tube as was formerly believed, but the muscle is attached to it only by a small amount of connective tissue."<sup>7</sup>

shown below that no such fixation of the soft palate is necessary for the action of the tensor upon the tubal wall.

Most writers, more from a consideration of the attachment of the tensor palati all along the membrano-cartilaginous wall of the tube than from actual physiological observations, are agreed that this muscle during contraction must dilate the tubal lumen, if not the orifice as well. There are, however, observers who oppose this view. Thus Cleland<sup>8</sup> in 1868, from his dissections and from observations upon the Eustachian tube in a case of destructive ulceration of the soft palate, was led to doubt the efficacy of the tensor palati as a dilator of the tube; and in 1878 Yule's studies<sup>9</sup> brought him to the same conclusion. Rumbold,<sup>10</sup> in the same year, believing from his experiments and clinical observations, that the walls of the tube are always in slight contact, was convinced that the tensor cannot dilate the tubal lumen. Fournié,<sup>11, 12</sup> in 1880, studied the action of the tubal muscles and, believing that the tube is normally open, regarded the tensor as an active constrictor of the Eustachian tube, having the function of closing the tube during deglutition. Bryant,<sup>13</sup> in 1907, discussing the action of the tensor on the basis of his anatomic and nasopharyngoscopic studies, wrote that "contractions of the muscle can affect the lumen of the tube but little, if at all." Mouret and Rouvière<sup>14</sup> believed that the tensor acts as a dilator of the tube, but sharply limited the action of the muscle to the superior portion of the tube, stating that its contraction can have no effect whatever upon the pharyngeal orifice, or the portion of the lumen immediately adjacent thereto.

Concerning the levatores palati muscles there also exists a considerable divergence of opinion. Toynbee<sup>4</sup> believed that the levator acts as a synergist to the tensor in its function of opening the Eustachian tube. Von Tröltzsch<sup>6</sup> concluded from his anatomical studies that this muscle is a constrictor of the tube, acting as an antagonist to the tensor, its belly during contraction pressing against the tubal wall and so tending mechanically to narrow the lumen. In 1862 Semeleder<sup>15</sup> (rhinoscopic observations) wrote that the levator, during contraction, narrows the pharyngeal orifice of the tube. Luschka,<sup>16</sup> in 1868, held that the levator closes the tube, and Cleland's observations<sup>8</sup> brought him to the same opinion. Politzer<sup>5</sup> believed that the muscle narrows the pharyngeal orifice but widens the lumen of the tube. Fournié,<sup>10, 11</sup> in 1880, described his experiments which led him to believe that the levator constricts the lumen of the tube. In 1903 Mouret and Rouvière<sup>14</sup> affirmed from anatomical considerations that the levator opens the pharyngeal orifice and the adjoining portion of the tubal lumen, while the remainder of the tube is dilated by the tensor palati, as has been already stated. They believed that only by the combined action of the two muscles could the tube be opened throughout its entire extent. In 1906, Panier<sup>17</sup> considered the levator as a tubal constrictor; while in 1907, Bryant<sup>13</sup> (anatomic studies and nasopharyngoscopic observations) regarded the levator palati as the muscle chiefly responsible for the opening of the tube and accordingly designated it as the "dilator tube," a name which had hitherto been applied to the tensor palati. Reference to con-

temporary texts leaves one uncertain. Piersol<sup>19</sup> writes: "In addition to opening the tube, the levator elevates its floor"; Spalteholz<sup>20</sup> gives as the action of the levator: It "narrows the ostium pharyngeum and widens the isthmus tubæ"; Cunningham<sup>21</sup> summarizes this diversity of opinion by the statement (quoted above) that some believe that, during swallowing, the contraction of the tensor opens the tube, while others hold that the contraction of the levator closes it during this act.

Whereas the greater part of the discussion concerning the movements of the Eustachian tube has centered about the tensor and levator palati, there have been experimenters and clinical observers who have insisted that other muscles may be concerned. Thus, according to Packard,<sup>22</sup> the palatopharyngeus muscle has an auxiliary action in the opening of the tube; and, indeed, Yule's studies<sup>23</sup> brought him to the view that this muscle is the chief tubal dilator, and that "the tensor and levator palati can have no participation in the opening of the tube." Gellé,<sup>24</sup> as a result of his own experiments, adds the superior constrictor of the pharynx to the list of muscles which have been regarded as dilators of the tube, while many authors speak hazily of the salpingo-pharyngeus muscle.

It is clear that further speculation, based upon anatomic grounds, or upon indirect physiological observations such as the attempts to interpret the functions of these muscles while they are hidden by the nasopharyngeal mucous membrane would be worth very little. In the present study the attempt was made, therefore, to lay bare all of these muscles in the living animal by careful dissection, leaving their nerve supplies intact; then, by electrical stimulation of the individual muscles, to determine the action of each upon the Eustachian tube; and finally, to observe directly their various actions during the reflexes which have been supposed to affect the Eustachian tube.

#### EXPERIMENTS

After preliminary tracheotomy and ligation of the carotids, the muscles about the Eustachian tube can be exposed for study in anesthetized dogs in the following manner: A midline incision is made through the mucous membrane of the soft palate and dissection is carried lateralward along the plane of the fibrous layer formed by the tendinous expansions of the tensores palati. The hamular process of the pterygoid bone is exposed and the palatopharyngeus muscle is seen, stretching from this point backward toward the pharynx. Careful separation of the fibers of this muscle from those of the closely associated pterygopharyngeus reveals the levator palati, which passes between them on its way to the soft palate, forming with them an angle of about 70°. The dissection is continued across the hamular process and the internal pterygoid muscle is seen just lateral to this landmark, extending anteriorly along the palatine bone. This muscle completely hides the tensor palati in such an approach. It is therefore necessary to remove the overlying fibers of the internal pterygoid in order to expose the tensor palati, which

can then be seen as a rather pale, very small muscle, the fibers of which extend from the pterygoid hamulus lateralward, backward and upward toward the inferior portion of the temporal bone. If a probe is now passed into the pharyngeal orifice of the Eustachian tube through an opening in the soft palate, the membrano-cartilaginous portion may be followed up to the beginning of the osseous portion, and the fibers of the tensor palati will be seen to be attached along the wall of the tube, the membranous side of which can be freely moved by traction upon this muscle.

Some observers have believed that the muscle fibers usually designated as the tensor palati are divisible, in reality, into two separate muscles, one having the function of making tense the soft palate, and the other that of opening the Eustachian tube. It is not possible by dissection, either in the dog or in human subjects, definitely to separate the tensor palati into two distinct muscles; and a microscopical study demonstrates that it is quite uniformly composed of striated fibers which are separated at no point by an intercalated epimysium. However, especially in dissections of formalin preserved specimens of dogs' heads, one is able to understand the basis of such a suggestion; for dissections may be made in which a portion of the fibers of the tensor appear to rise from a firm attachment to the hamular process of the pterygoid bone and to be inserted along the membranous wall of the tube, while the remaining fibers arise from the skull adjoining the osseous portion of the tube and converge into a tendon which glides, freely movable, over the hamular process to expand into its fibrous insertion in the soft palate. Both portions of the muscle, however, are enclosed in the same facial sheath.

In the dissections made upon the anesthetized animal for experimental studies, care was taken to leave uninjured the nerve supply of each muscle. The integrity of the nerve supply was, in all cases, tested after completing the dissection by watching for the contraction of the individual muscles during the execution of the swallowing reflex in which they normally participate.

In such a vivisection as has been described, the muscles in the region about the Eustachian tube may be stimulated electrically either individually or in groups, and their respective actions upon the tube may be directly observed; for the entire region, containing the various muscles (naked throughout their extent), and the pharyngeal orifice of the tube as well, lies clearly exposed before the eyes.

The internal pterygoid is the largest of the muscles which lie near enough to the tube to suggest a possibility of action upon that structure. Its close apposition to the tensor palati, and so to the membranous wall of the canal, has already been mentioned; and it is an interesting fact that both Eustachian tubes of birds open into the midline of the pharynx through a single, common membranous canal, the patency of which is governed physiologically by the action of the adjacent internal pterygoid muscles.<sup>25</sup> Further, it has been held that, in man, the Eustachian tubes may be opened by protrusion of the lower jaw (*i. e.*, by contraction of the internal pterygoids). This muscle was therefore stimulated in the dog, but its con-

traction was seen to be entirely without effect upon the pharyngeal orifice of the tube.

Stimulation of the palatopharyngeus, the pterygopharyngeus or the superior constrictor muscle of the pharynx causes no change in the condition of the tubal orifice.

Stimulation of the levator palati muscle does not affect the orifice in any way. There occurs, during its contraction, no dilatation whatever, nor is there seen the narrowing of the orifice which has been assumed to result as a theoretical effect of the bulging of this muscle during contraction. The only effect of the contraction of this muscle (aside, of course, from its action upon the soft palate), which can be observed by inspection of the nasopharynx, is a disturbance of the mucous membrane immediately overlying its belly. This is seen when only the lateral surface of the muscle is exposed for stimulation.

When the tensor palati is stimulated, its contraction is accompanied by a wide gaping of the pharyngeal orifice of the tube and a tension of the fibrous expansion of its tendon in the soft palate. It can be seen that this latter effect does not actually modify the condition of the soft palate very much, for it appears to be concerned chiefly with that portion which is immediately adjacent to the hard palate—the so-called "fibrous prolongation of the hard palate" mentioned by Henle; and this "fibrous prolongation" possesses a definite stiffness even when the tensor palati is at rest. The dilatation of the tubal orifice is clearly seen to be caused by the muscle, during its contraction, pulling against its attachment to the membranous wall of the tube, and so drawing this portion away from the cartilaginous wall with which it lies in contact in the resting condition. Henle<sup>2</sup> believed that the tensor opens the tube by its action upon the upper, hook-like portion of the cartilaginous wall. Undoubtedly the tensor has fibers of attachment along this cartilaginous border as well as along the membranous wall of the tube and it is possible that these fibers may actually unfold this scroll-like border to some extent. However, one can clearly see that it is the lower margin of the orifice which is most widely dilated during the contraction of the tensor palati; and it is also distinctly seen that the muscle lifts the membranous wall away from the cartilaginous chiefly by simple traction upon it.

Von Tröltzsch, in his discussion of the physiology of the Eustachian tube,<sup>3</sup> suggests the following theory to explain the action of the tensor (and levator) palati upon the tube: "During deglutition the soft palate, through the action of the lower muscles (glosso-palatine and pharyngo-palatine), is stretched downward and back and is pressed against the posterior wall of the pharynx. But a contraction occurs simultaneously in the antagonists of these muscles, the upper muscles of the palate (tensor and levator palati), which will change points of fixation and attachment in such a way that the soft palate will become the (relatively) fixed point, and the movable wall of the tube the point of origin of the muscular fibers from which motion proceeds." Jago<sup>4</sup> also laid stress upon such a "fixation" of the soft palate as a necessary precursor to the action of the tensor palati. In the present experiments, however, the palatal insertion of the tensor was

found to be quite unessential to the dilatation of the tube; for the fibrous expansion of the tendon of this muscle may be cut through in its entire extent, eliminating any possibility of its action as a "fixed point," and nevertheless stimulation of the tensor or its contraction during the swallowing reflex will cause quite as wide a dilatation of the tubal orifice as that which occurs when the palatal insertion is left intact. The attachment of the tensor palati to the hamular process of the pterygoid bone seems to be the only fixed point necessary for the action of this muscle upon the tube; and, indeed, Von Tröltzsch himself has remarked upon the extraordinary strength of this attachment. Moreover, the fact that stimulation of the levator palati failed to cause any change in the condition of the tubal orifice cannot be said to be a result of a lack of "fixed point" in the palate against which this muscle might pull; for the palatal insertion of the levator has been grasped with forceps and held immovable during stimulation of the muscle, and, although in some cases actual traction was exerted upon the palatal insertion, the tubal orifice remained entirely unaffected during the most vigorous contractions of the muscle.

That the tensor palati alone effects the dilatation of the tubal orifice was determined by cutting in turn the palatopharyngeus, the levator palati and finally the tensor palati, while the effect of the swallowing reflex upon the orifice was observed after the severance of each muscle, all of which normally contract during deglutition. The orifice was widely opened during each swallowing reflex with no appreciable variation in extent until the tensor had been cut, whereupon the reflex was no longer accompanied by the slightest opening of the tube. The experiment was then reversed; the tensor having been cut first, the swallowing reflex was accompanied by no dilatation of the orifice whatever, although both of the other muscles were intact and contracting vigorously. A similar type of experiment was performed by stimulating the muscles electrically; and it was found that stimulation of the tensor alone, after cutting the two other muscles caused a wide gaping of the pharyngeal orifice of the tube; whereas, if the tensor were cut first, the most forceful contractions of the palatopharyngeus and the levator palati (either individually or synchronously) were entirely without effect upon the orifice. These experiments demonstrate that no muscle except the tensor palati exerts any influence upon the pharyngeal orifice of the Eustachian tube, and there is no suggestion that the other muscles of the region act as auxiliaries or antagonists to the tensor in its function of opening the tube; for during deglutition there was no variation in the degree of dilatation of the orifice whether the levator palati and palatopharyngeus muscles were severed or were left intact.

The preceding experiments are concerned with the movements of the pharyngeal orifice, and it has been shown that the levator palati plays no part in the regulation of the patency of this portion of the Eustachian tube. It was, however, necessary to try to determine what effect, if any, is exerted by this muscle upon the lumen or isthmus of the canal, to which it is certainly closely related anatomically,

although, as has been pointed out,<sup>24</sup> the muscle does not actually arise from the tube, but is connected with it through an interposed layer of fibrous tissue.

According to one view, it will be remembered, the levator dilates the lumen of the tube by elevating its floor.<sup>19, 24, 25</sup> Another opinion is that the contracting belly of the levator narrows the lumen of the tube by mechanical pressure.<sup>8, 23, 26</sup> Dissections make it appear doubtful that the cartilaginous wall of the tube to which the levator is related can actually be displaced to any extent by the contraction of this muscle. But an attempt was made to study directly the conditions existing within the Eustachian tube during the contraction of the various muscles about it. A manometer was constructed in the following manner: A very small cylindrical balloon, made from very thin sheet rubber, was sealed to a piece of glass tubing bent to suit the direction of the tubal orifice. By means of small-bore rubber tubing, this balloon was placed in communication with a second balloon about the size of an olive, which was situated within an air-tight chamber having a single outlet, from which a second piece of tubing led to the tambour of a delicate compound lever. By means of a



FIG. 1.—Kymographic record. Manometer downward deflections indicate widening of tubal lumen. X = Stimulation of tensor palati. o = Stimulation of levator palati.

T-tube and a stop-cock between the terminal balloon and the encased balloon, both could be inflated to the desired extent; while a second T-tube and stop-cock between the balloon chamber and the tambour, when open, allowed air to be introduced into the first portion of the system without any displacement of the lever; after which it could be closed so that then any displacement of air, however slight, from the little cylindrical balloon, would in turn cause a displacement of air from the chamber into the tambour with a consequent deflection of the sensitive lever. The little terminal balloon, after inflation, was introduced into the Eustachian tube. This was accompanied, of course, by some displacement of air from the balloon, as the walls of the tube tended to close down upon it. Care was taken to see that the pharyngeal orifice was occupied by the glass tube, and that the balloon was allowed to lie entirely within the Eustachian tube, thus eliminating any effect of the movements of the ostium. The hope was that when the various muscles were now stimulated, any change occurring in the size of the lumen would cause air either to pass into or to be driven out of the terminal balloon, and that such a change would be recorded by the lever. The chief difficulty in such an experiment lies in the fact that the introduction of air necessary to inflate the balloon causes sufficient pressure to distend the tube mechanically; and many attempts were made with different degrees of inflation before any trust-

worthy results could be obtained. In several experiments, however, it was found possible to obtain kymographic tracings in which downward deflections of the lever indicate distinctly a widening of the tubal lumen during contractions of the tensor palati (Fig. 1); nor was there any variation in the extent of the excursion of the lever, whether the levator palati and palatopharyngeus muscles were cut or intact, at rest or contracting simultaneously with the tensor. Stimulation of these latter muscles, and also of the internal pterygoid and superior constrictor of the pharynx, while the tensor palati was at rest, caused not the slightest deflection of the lever in any experiment.

It has been noted by otologists,<sup>8, 12</sup> that a catheter introduced into the Eustachian tube rotates somewhat during deglutition. This movement has been believed to be caused by the change in the shape and caliber of the lumen resulting from muscular action upon the tube, especially through the effect of the levator palati.<sup>3</sup> The phenomenon was here utilized in the attempt to corroborate the manometer experiments. A long, very light straw with a base several millimeters in diameter was introduced into the tube through the pharyngeal orifice. The length of the straw exaggerated the movements of the end within the tube sufficiently to permit satisfactory kymographic tracings to be obtained from the free end. On stimulation of the tensor palati muscle there occurred a marked deflection of the straw. When the internal pterygoid, the levator palati or the palatopharyngeus muscles were stimulated, the straw remained absolutely at rest. Certainly, if the levator palati had caused any change in the caliber of the lumen or position of the walls of the tube (if, for example, the floor had been vigorously elevated as has been assumed<sup>19, 25</sup>), the straw would have suffered some displacement.

These experiments lead us to the conclusion that the tensor palati muscle alone is responsible for any change that may occur physiologically in the patency of the pharyngeal orifice or lumen of the Eustachian tube. This conclusion was supported by nasopharyngoscopic observations made upon a patient in a ward of The Johns Hopkins Hospital. This man had suffered from a unilateral paralysis of the tensor palati muscle following disease of the fifth nerve. The pharyngeal orifice of the tube on the affected side appeared somewhat more patent than that of the normal side; and during deglutition, the unaffected tube gaped normally, while the orifice on the side of the tensor paralysis remained quite stationary, although the levator palati, palatopharyngeus and superior constrictor muscles were contracting vigorously.

#### CONCLUSIONS

1. Normally, the Eustachian tubes are closed. They are opened during the swallowing, yawning and sneezing reflexes. They exhibit no independent reflex dilatations either periodic or irregular. Normally, they are not opened by respiratory movements, either quiet or forced, and are unaffected by mouth-breathing or by simple elevation of the soft palate (produced by contraction of the levatores palati alone).

2. Although a most important function of the Eustachian tube is that of equalizing the atmospheric pressure on both sides of the tympanic membrane, the mere existence of a disturbed pressure equilibrium will bring about no regulatory reflex dilatation of the tube, either independently or through the swallowing reflex. Deglutition, as a means of restoring pressure-equilibrium to the ear-drum, is performed, when necessary, consciously or through habit; but this reflex is never set in motion directly by the stimuli arising from tension of the tympanic membrane.

3. The levator palati, the palatopharyngeus, the internal pterygoid and the superior constrictor muscle of the pharynx (each of which has been variously described as a dilator or constrictor muscle of the Eustachian tube), were found to exert, by their contractions, no influence whatever upon the patency of the orifice or lumen of the tube.

4. The tensor palati is the only muscle which is functionally related to the Eustachian tube. Contraction of this muscle is always accompanied by a dilatation of the tubal orifice and lumen. There exists no constrictor muscle of the tube. Relaxation of the tensor palati is followed by a passive return of the tubal walls to the condition of approximation which they normally occupy when at rest.

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## HEREDITARY SPASTIC PARAPLEGIA

By V. R. MASON and W. F. RIENHOFF, JR.

*(From the Medical Clinic, The Johns Hopkins Hospital)*

The four cases of hereditary spastic paraplegia which form the basis of this report are of interest chiefly as examples of a rare hereditary alteration of the central nervous system which has affected members of one family for three generations. The cases differ in minor details from others that have been reported, but in general may be considered as fairly typical instances of the disease.

**CASE 1.**—Mary Rexroth. Although this woman was not examined by us, a fairly satisfactory description of her symptoms was obtained from members of her family.

She was married at an early age to a healthy man and gave birth to five children, all by easy labor. Two of the children (Case 2 and Case 3) are afflicted with a malady which they believe is similar to that from which their mother suffered. As far back as the informants can recall, her voice was shaky and tremulous, making speech almost unintelligible. She also had a coarse tremor of the arms and hands, which prevented writing and made the

The hearing is acute. The tongue is protruded in the mid-line, but is tremulous. On speaking there is a coarse tremor of the tongue and jaw which produces staccato, mousy speech.

All of the muscles of the trunk and extremities stand out prominently and resist pressure. The legs and, to a less extent, the arms are spastic. There are a few coarse fascicular twitches of the muscles. Muscle strength is fair in the arms, diminished in the legs. There is a continuous coarse tremor of the hands and arms which becomes much more marked on volitional effort (Fig. 1). There is also a coarse tremor of the lower extremities, only, however, when purposeful movements are attempted.

Sensation is intact. The sphincters function normally. The tendon reflexes are exaggerated, especially in the lower extremities. There is a marked jaw-jerk. No clonus. Bilateral Babinski phenomenon. Abdominal reflexes present. The gait is typically spasto-paretic with a tendency toward a scissor-gait. There is slight bilateral pes equino-varus. The patient shows no ataxia, dysdiadokokinesis, or disturbances in knee-heel and finger-nose tests, except those dependent upon intention tremors.

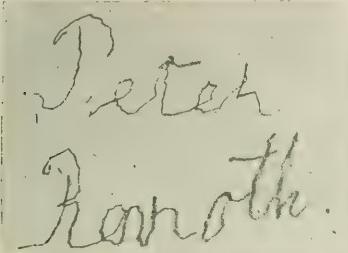


FIG. 1.—Handwriting of Case 2.



FIG. 2.—Handwriting of Case 3.

use of table utensils very difficult. Her legs were stiff and she dragged her toes while walking. These symptoms grew gradually more pronounced until she became, in later life, practically bedridden. Intelligence was unimpaired and there were no sphincter disturbances. She died at the age of 75 of heart disease.

**CASE 2.**—Peter Rexroth. This patient is the son of Mary (Case 1) and a brother of William (Case 3). Aged 61, machinist. He married at the age of 19 years. Of his children one daughter is affected with the same malady (Case 4) and one son is mentally inferior and incorrigible.

**Present Illness.**—At about the age of 14 patient noticed that he could not run as fast as other boys. Soon afterward tremors of the hands made writing difficult and his voice became tremulous as a result of the "jerking" of his lips when speaking. This was followed by stiffness of the legs and dragging of the feet. The symptoms have gradually become intensified and now it is only with difficulty that he can walk alone.

**S. P.**—The patient is well developed and well nourished. He is mentally alert and answers questions intelligently.

The pupils are equal, regular, and active to light and on accommodation. There are slight nystagmoid jerkings of the bulbs on lateral deviation; otherwise the extra-ocular movements are normal. Ophthalmoscopic examination shows the fundi to be normal.

**Laboratory Examinations.**—B. P. 125/75. R. B. C. 4,408,000. W. B. C. 8360. Hgb. 60 (Sahli). Differential P. M. N. 72 per cent; S. M. 20 per cent.

The blood Wassermann test negative. Phthalein excretion 55 per cent in two hours.

C. S. F.: Normal pressure. One cell per c. mm. Globulin not present. Wassermann test negative. Gold sol curve negative.

X-Ray: Spine, slight arthritis. Gastro-intestinal tract, negative. Stool negative. Urine not remarkable.

**Summary.**—Spastic paraplegia, with coarse tremor of arms and hands, markedly accentuated by intentional movements. There is staccato speech dependent upon spontaneous and intention tremor of the jaw and tongue.

**CASE 3.**—William Rexroth. This patient is also a son of Mary (Case 1) and a brother of Peter (Case 2). Aged 68; barber.

He first began to notice stiffness and weakness of the legs at the age of 14, and soon afterward tremors of the hands and jaw.

**S. P.**—The patient is of normal intelligence and well developed physically. The pupils are active, the fundi and the extra-ocular movements are normal. There are tremors of the jaw and tongue, very marked during speech, and producing a jerky, staccato intonation. There is also a coarse, irregular tremor of the hands and arms, accentuated by purposeful movements (Fig. 2), but also present during rest.

The tendon reflexes of the arms, and more especially of the legs, are hyperactive. No clonus. Plantar response is normal. Abdominal reflexes present.

The gait is spasto-paretic, but there is no ataxia. Some loss of power of the legs can be demonstrated.

Sensation is intact. No sphincter disturbances.

*Summary.*—Spastic paraplegia with intention tremor of jaw, tongue, and arms.

CASE 4.—Margaret Rexroth, aged 26. Daughter of Peter (Case 2).

The birth was normal, the labor easy; the mother is perfectly healthy. The patient learned to walk at the age of two. At 4 years of age she began to drag the right foot slightly. She started to school at the age of 7 but at 14 had reached only the second grade. During this period her speech became affected and she tripped and fell frequently. In 1914 she could walk with assistance but the gait was very stiff and unsteady.

S. P.—November, 1914 (patient aged 20). The patient is well developed. The mentality is impaired. The Binet-Simon age is 9 years. The cranial nerves function normally. Fundi normal. Speech is disturbed, due to mousing of words. There is a constant coarse tremor of the hands and arms. Tendon reflexes are all exaggerated. Patellar and ankle clonus can be elicited. The plantar response is equivocal.

Examination in February, 1920. All of the symptoms have progressed since the above recorded examination. A remarkable coarse, jerky tremor of the hands, arms, jaw and tongue is constantly present and markedly accentuated by purposeful movements. Speech staccato and difficult to understand. *Third riding artillery brigade* is repeated. "*Third riling tullary bade*"; *Metho-dist Episcopat*, "*Mest piscal*." The legs are very spastic. The tendon reflexes are all exaggerated, especially in the lower extremities. There is a patellar and an ankle clonus on each side. The Babinski phenomenon is equivocal.

The patient is now unable to walk and there is marked disuse atrophy of the leg muscles. The sphincter muscles function normally and sensation is not impaired.

*Summary.*—Spastic paraplegia. Mental inferiority. Intention tremor of arms. Speech disturbance.

Strümpell,<sup>1</sup> in 1880, reported two cases of hereditary spastic paraplegia, and although at the time he was not certain of the exact nosology of the symptom-complex, he had an opportunity a few years later to examine the central nervous system of one of his patients and to demonstrate the pathological basis of the syndrome. Since then the records of about sixty affected families have appeared in the literature and are summarized by Lorrain<sup>2</sup> Delaréde and Minet,<sup>3</sup> Bono,<sup>4</sup> and Rhein.<sup>5</sup>

Usually, the malady affects individuals in only one generation but in seven of the families recorded characteristic symptoms of the disease were present in more than two generations. Our own cases offer still further proof of the true hereditary character of this type of degeneration of the central nervous system.

Etiological factors, other than heredity, are not known. In a few instances, however, there was consanguinity and in others the parents of the patient were either feeble-minded or presented certain anomalies of development or signs of degeneracy. The relation of these factors to the hereditary occurrence of degeneration of the central nervous system is not understood fully at the present time. A critical summary of the subject will be found in a recent article by Jendrassik.<sup>6</sup>

The age at which symptoms of the affection first appear is not constant. Strümpell<sup>1</sup> stated that there was a juvenile form beginning at about puberty, and an adult form which usually appears during the fifth or sixth decade. Since the time of his report cases have also been observed in infancy and early childhood. It is therefore apparent that symptoms of the disease may become manifest at any age, although it is characteristic of hereditary diseases of the central nervous system that the age of onset is about the same in individuals of the same generation.

So far as the reported cases show, there is no evidence that sex plays any important rôle, either in the occurrence or in the transmission of the disease. The cases herein recorded are divided equally as to sex; moreover, the disease was transmitted once by an affected female and once through an unaffected female.

The fundamental symptom, from which the disease derives its name, is a spastic paraparesis which may involve the upper extremities to some extent after the condition has progressed for many years. Upon this basic symptom one or more of an array of subsidiary symptoms are usually engrafted. The most important of these are tremor of the tongue, as a rule intentional in type, disturbances of speech, optic atrophy, nystagmus, ocular palsies, bulbar disturbances, scoliosis, pes equino-varus, ataxia, muscular atrophies, and occasionally some mental impairment. Sensation is usually unaffected, as are also the sphincter functions.

It is not possible to group the reported cases into rigid clinical types on account of the variety of syndromes which have occurred from combinations of the symptoms enumerated above. In a few cases the patients have presented only a spastic paraplegia; in the greater number, however, the symptomatology has approached that commonly observed in hereditary ataxia of the Friedreich or Marie type, and indeed in not a few instances a differential diagnosis has been difficult or impossible. Such cases have been regarded by some neurologists as transition forms between the spastic and the ataxic degenerations of the nervous system—a point of view expressed by Jendrassik and, as we shall see farther on, supported by certain clinical and histological evidence.

In the first place, the etiology of the three diseases is identical and the clinical course essentially the same. They all begin usually about puberty, progress slowly to a certain point and then remain stationary. Moreover, typical or "pure" cases of any of the three affections are rare. This is especially true of Marie's ataxia, in which the symptomatology may resemble Strümpell's paraplegia, on the one hand, or Friedreich's ataxia on the other, and therefore may be considered as a transition form between the spastic and the ataxic types. Furthermore, even in rather typical cases of one of the diseases, symptoms common to all three, such as nystagmus, tremor, or pes equino-varus, have been observed.

Secondly, the pathological anatomy of three afflictions, although not at present fully understood, is in many respects strikingly similar. As a rule, there is in each disease a well

marked combined sclerosis of the postero-lateral tracts of the cord, of the type characteristic of hereditary degenerations of the nervous system. The extent to which the several tracts are involved, however, varies in the individual cases in accordance with the symptomatology. Thus, in spastic paraplegia the posterior tracts and cerebellar tracts may be only slightly involved, while the pyramidal tracts are markedly affected. In Friedreich's ataxia, on the contrary, the pyramidal tracts may be but slightly altered. The pathological basis of Marie's ataxia is somewhat more complicated. In certain instances only a diminution in size of the cerebellum and cord was observed, while in other cases there was also a well marked sclerosis of cord tracts of the same character as that found in the other hereditary degenerations.

Certain other alterations not characteristic of any of the three maladies have also been observed in many cases. The most important of these are diminution in the number of fibers in the white tracts of the cord and the number of Betz cells and anterior horn cells. In some cases, also, the whole central nervous system has appeared to be unusually small. In general, these changes have been observed as frequently in the spastic as in the ataxic forms of hereditary degeneration.

There is much evidence, therefore, to support the assumption that the hereditary degenerations of the nervous system, characterized by ataxia (Friedreich's ataxia) alone, ataxia and paraplegia (Marie's ataxia), and paraplegia alone (hereditary spastic paraplegia) are all syndromes or clinical forms of the same morbid entity. The definite proof of the validity of this assumption, however, can be adduced only by a more complete correlation of clinical and pathological studies than is possible at the present time.

**Diagnosis.**—The differential diagnosis from multiple sclerosis is often difficult on account of the similarity of symp-

tomatology; but the familial occurrence of the disease and the absence of remissions is of help in excluding disseminated sclerosis. Furthermore, changes in the cerebrospinal fluid, commonly present in that disease, have not been found in the few cases of hereditary spastic paraplegia in which lumbar puncture has been performed.

Isolated instances of hereditary spastic paraplegia probably occur. The diagnosis of such cases in the absence of a familial or hereditary history would be doubtful at best. Moreover, it would be necessary to exclude the commoner causes of spastic paraplegia.

From Friedreich's or Marie's ataxias differential diagnosis is largely of academic interest. In some instances it is impossible, but in the majority, if the presence or absence of spastic paraplegia or ataxia is employed as the basis of differentiation, it is possible to place the disease in its proper group. There will always, however, be some cases which are best classified as transition forms.

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### A STRIKING ELEVATION OF THE TEMPERATURE OF THE HAND AND FOREARM FOLLOWING THE EXCISION OF A SUBCLAVIAN ANEURISM AND LIGATIONS OF THE LEFT SUBCLAVIAN AND AXILLARY ARTERIES

By WILLIAM S. HALSTED

In a series of signally interesting papers Professor René Leriche calls attention to the value of what he terms perirterial sympathectomy in the treatment of various neuralgias, local ischemias, reflex contractures of the Babinski-Fronten type, and other affections. Fostered in the traditions of the schools of Magendie, Claude Bernard, and Brown Séquard, it was in the happy order of things that it should fall to the lot of a surgeon of Lyon to turn to therapeutic account a discovery of the greatest of the founders of experimental medicine. A devoted disciple of Jaboulay, Leriche credits this talented surgeon, his "master," with the suggestion which led to the novel and important researches made by him during the years of the war.

My interest in Leriche's work has been reawakened by an observation made only a few weeks ago in the Surgical Clinic of The Johns Hopkins University. In 1918 I ligated the left subclavian and carotid arteries near their origin from the aorta for the cure of a huge subclavian aneurism (Figs. 1 and 2). For a year the aneurism decreased steadily in size (Figs. 3, 4, 5 and 6). Then for a year we lost track of the patient. About two months ago we succeeded in tracing him, and persuaded him to let us excise the aneurism, which

in the period of non-observation had developed a faint pulsation and become slightly larger (Fig. 7). About four hours after this operation, at which the aneurism was excised and the subclavian and axillary arteries ligated, it was noticed that the left hand and forearm, which for two years had been strikingly cold, had become abnormally warm—appreciably warmer than the corresponding limb. Unfortunately, our surface thermometer had been broken and we were unable to obtain another. About five weeks after the operation the hand and forearm became cold again—at first in small areas—remaining cold for only a day or two.

To-day (June 28) the 69th since the operation, the back of the left hand is quite cold, whereas the left palm is about as warm as the right. The temperature of the hand and forearm has varied from day to day and from hour to hour; certain small, quite well-defined areas have remained uniformly cool; otherwise, the hand and forearm have maintained their normal warmth.

SUR. NO. 46179. Alexander Miller. Negro, at. 29. Admitted to The Johns Hopkins Hospital April 22, 1918; discharged August 12, 1918.

The patient states that he has always been perfectly well. In April, 1917, he noticed a swelling about the size of an egg above

the left clavicle. Almost simultaneously with the recognition of the swelling, pain and numbness in the upper extremity were observed. The growth of the tumor was gradual until about March, 1918; since then it has been very rapid. For the past two weeks the limb has been totally paralyzed. The patient recalls that until Christmas, 1917, he could still raise his arm a little.

About four years before admission the patient was shot just above the left clavicle. The wound healed promptly. The bullet was not removed and has given him no indication of its presence.

*Examination.*—The patient is evidently suffering severe pain, and constantly supports his left wrist with his right hand. The pain, he says, is most intense from the elbow-joint to the hand and in the left shoulder.

A huge aneurism occupies the left neck from the clavicle to the ear (Figs. 1 and 2). The head is deflected and rotated to the right. The vertex of the pulsating mass is about on a plumb-line dropped to the junction of the middle and inner thirds of the clavicle. The swelling and pulsation extend on to the chest, and the whole body is jarred with each heartbeat. Posteriorly the diffuse pulsating tumefaction spreads out to a point below the spine of the scapula. The aneurism extends upward in dome-shape; a hand can be inserted between it and the face down to the angle of the lower jaw. The whole shoulder girdle appears to be raised away from the chest wall, the acromio-clavicular articulation being apparently disrupted. The skin over the tumor is very tense and glistening. From the clavicle to about the level of the nipple the brawny tissues are probably infiltrated with blood as well as inflammatory products. The trachea is displaced to the right. A systolic bruit, most distinct above the inner third of the clavicle, can be heard over the greater part of the pulsating mass. No thrill can be felt. The left radial pulse is absent. There is slight ptosis of the left eyelid, but the pupils respond equally. Only the inner third and the acromial tip of the clavicle can be defined with the fingers. The remainder of the bone is buried in the tumefaction. A bullet is palpable just beneath the skin to the left and below the spine of the seventh cervical vertebra. The left arm is paralyzed. The extent of the loss of motion and sensation and the degree of restoration of function will be outlined in a subsequent paper.

*Fluoroscopic Examination.*—The shadow of the aneurism extends to the lower border of the clavicle but not to the first rib. The heart seems not to be enlarged. The right subclavian and carotid arteries, distinctly seen, are normal in size.

*Skiagraphic Report.*—Large mass in left neck. Clavicle deeply eroded, perhaps fragmented. Bullet in upper dorsal region.

*Operation.*—April 26, 1918. Dr. Halsted. *Ligation of the left common carotid and the left subclavian arteries near their origin from the aorta.*

Ether. Wide protection of the operative field with celloidin-silk.<sup>1</sup> Transverse bow-incision just below the cervico-thoracic junction, supplemented by a vertical one along the left border of the sternum (bow and plummet incision). Free exposure of manubrium and left sterno-clavicular joint. The incised tissues were edematous, particularly so below the clavicle. The superficial vessels were abnormally large. Careful hemostasis by the fine silk transfixion method. The left two-thirds of the manubrium and the left sterno-clavicular joint were resected with the giant rongeur forceps of Esmarch, care being taken to avoid disturbing the fragments of the eroded clavicle. The thymus gland and the left innominate vein were drawn upward and to the right with a retractor.

The trachea in the thorax as well as in the neck was displaced to the right by the pressure of the aneurism. The left carotid,

deeply situated and occupying the midline in the chest, was gently occluded with a tape ligature. This artery was thought at first to be the left subclavian inasmuch as, according to the erroneous testimony of an assistant, its occlusion did not affect the pulse in the left temporal artery, and lessened the force of the pulsation in the aneurism. To obtain access to the left subclavian artery the cartilage of the left first rib and the adjoining margin of the sternum were cut away. The arch, the aortic isthmus and descending aorta, and the left auricle of the heart were palpated with the finger of the operator before the left subclavian, lying close to the vertebral column, was identified. With the aid of four long, narrow dissectors, two of which were manipulated by the operator and two by Dr. Mont Reid, the vessel was clearly exposed at its origin from the aorta and for several centimeters distal to this point. As it was evident that none of the various aneurism needles was suitable for the passage of a ligature at this depth, a long, narrow, blunt dissector, slightly curved and pierced at its tip, was armed with fine silk and passed under the artery. By means of this thread and then another, linen tapes were drawn under the subclavian; both of these were tied, the second distal and close to the first, with force only sufficient to close completely the artery's lumen. The aneurism became very tense and hard immediately after the ligation, but was pulseless.

The patient's condition, bad on admission and particularly so just before operation, caused us some anxiety. Traction within the thorax on the branches of the aortic arch or on the pulmonary artery affects unfavorably and eventually disastrously the action of the heart. The pulse, about 120 at the beginning, was 140+ and quite weak at the termination of the operation. The wound was completely and accurately closed with interrupted sutures of fine silk. A large dead space in the mediastinum was, naturally, unavoidable.

#### Healing *per primam*.

November 9, 1918. The patient has been examined frequently since his discharge from the hospital. There has been no pulsation in the aneurism since the operation. The mass has steadily but slowly decreased in size. The patient can make slight movements with the left fingers, otherwise there has been no appreciable return of power or sensation in the paralyzed arm.

The patient was observed frequently throughout the year following the operation. Slowly but steadily the pulseless tumor, during this period, diminished in size. Then for a year the patient, living out of town, was lost sight of. Exactly two years after the first operation he returned, at our solicitation, to the hospital. Now for the first time since the operation a very faint pulsation was discernible. The tumor (Fig. 7) measured in its transverse (frontal) diameter precisely the same as when last seen a year before; the antero-posterior measurement (sagittal), however, gave an increase of about 4 c. m. I decided that the aneurism should be excised, and on the 20th of April, 1920, performed the operation as follows:

The skin over the tumor and a wide area about it were protected with Chinese silk dipped in celloidin. The incision, made through the tightly adherent silk, ran with the clavicle in its central part, curving up into the neck at its inner end, and down along the cephalic vein at its outer. Superimposed on and not attached to the greatly broadened and thickened clavicle was a sharply convex bow of bone about 9 cm. long and 6 mm. thick. This bow, recognizable in the photograph (Fig. 5), was cut away and the clavicle bitten through with a heavy rongeur forceps at two points as close to the aneurism as possible. The cephalic vein was divided, and the axillary artery—pulseless, reduced in

<sup>1</sup> W. S. Halsted. Clinical and Experimental Contributions to the Surgery of the Thorax. *Trans. Amer. Surg. Assn.*, 1909, xxvii, p. 111.



FIG. 1.—Aneurism of the left subclavian artery.  
Alexander Miller, April 22, 1918.



FIG. 2.—Alexander Miller, April 22, 1918.



FIG. 3.—Alexander Miller, 109 days after ligation of  
the subclavian artery near its origin.



FIG. 4.—Alexander Miller, 109 days after the ligation.

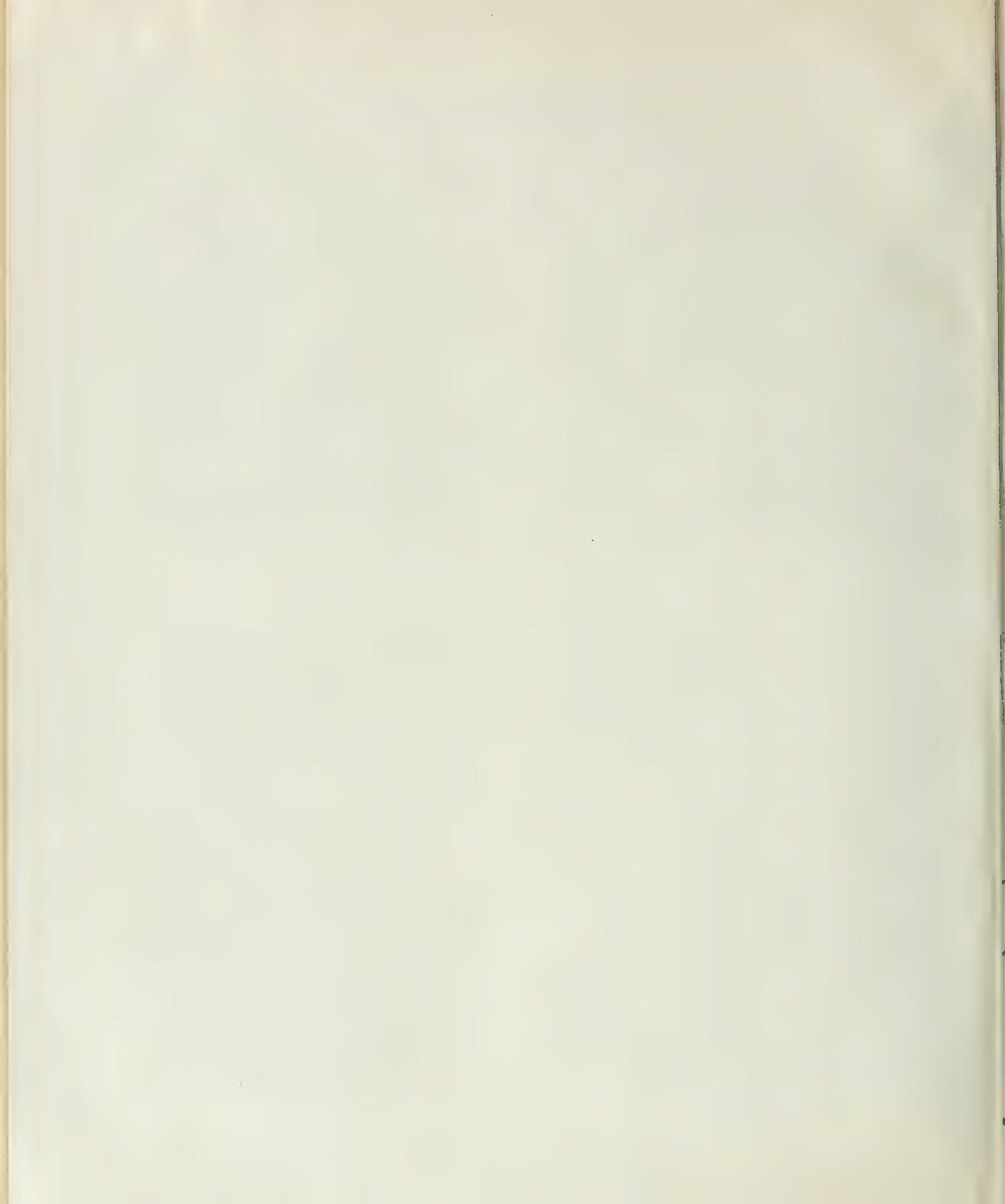




FIG. 5.—Alexander Miller, 10 months after the ligation



FIG. 6.—Alexander Miller, 10 months after the ligation.



FIG. 7.—Alexander Miller, 2 years after the ligation  
of the subclavian, and 2 weeks before the excision of  
the aneurism.



FIG. 8.—Alexander Miller, 1 month after excision of  
the aneurism.



size, but not empty—was ligated about at the junction of its first and second portions, through a split made in the pectoralis minor muscle; the third portion of the subclavian artery was ligated above the clavicle; the aneurismal sac, and the resected rib were excised in one piece. The aneurism was matted almost everywhere to the surrounding parts by dense connective tissue, and hence had to be carved out rather than enucleated. The identification and freeing of the roots of the brachial plexus, which were in places embedded in the wall of the sac, consumed much time. The operation was conducted in a bloodless manner until nothing remained to be done except to divide the narrow neck of the sac. The tissues of this neck proved to be thin and friable, and the patient lost a few cubic centimeters of blood through the slit in the artery—the mouth of the false sac—which was readily closed with three stitches of fine silk. The wound was closed without drainage. I am greatly indebted to Dr. Heuer and Dr. Reid for their skillful and highly competent assistance which enabled me without concern to conduct the operation to a satisfactory conclusion.

At the first dressing, made on the 10th day after operation, it was noted that a little fluid had accumulated in the outer part of the wound. This was evacuated by puncture with a wooden toothpick wrapped with a few fibres of cotton dipped in pure carbolic acid. Closure of the puncture was prevented by the reapplication of the acid in the same manner on two alternate days. The introduction of a drain of any kind we scrupulously avoid. The word "drainage-tube" is in disfavor in our clinic. Should a wound become infected, tubes would be properly introduced for the purpose of disinfection, but not for drainage.

Noteworthy is the fact that the patient's hand and forearm, which prior to and ever since the first operation had been markedly cold, became strikingly warm about 4 hours after the second operation and have remained warm, except in certain areas, to the present time (June 28). It is improbable that the ligation of the cephalic vein was in any part responsible for this indubitable improvement in the circulation. The elevation of the temperature of the hand and forearm must, I believe, be attributable to vasodilatation incident to the ligations of the subclavian and axillary arteries—to the crushing of their nerves. This question will be discussed in the course of the consideration of the treatment of subclavian aneurisms in a paper about to appear in *The Johns Hopkins Hospital Reports*.

I have found pleasure in translating one of the papers of Monsieur Leriche, believing that his work on periarterial sympathectomy will at this moment particularly interest surgeons who may have the opportunities and the inclination to verify his observations. While disclaiming unqualified acceptance of some of his explanations and deductions which are at variance with the teachings of physiologists we must recognize that Leriche's contributions are of unusual interest and value; they will stimulate investigation.

#### PERIARTERIAL SYMPATHECTOMY AND ITS RESULTS

RENÉ LERICHE

In January, 1916, and in April of the same year,<sup>2</sup> I made known the first results which the denudation and excision of the sym-

<sup>2</sup> R. Leriche: De la causalgia envisagée comme une névrite du sympathétique et de son traitement par la dénudation et l'excision des plexus nerveux péri-artériels. Société de Neurologie, 6 Janvier 1916; La Presse médicale, 20 Avril 1916.

pathetic plexuses around the arteries in causalgia and in certain trophic troubles had given me. Since then this operation has been tried in various ways. Le Fort, Cotte, Sencert, Lavenant, de Massary and Veau, Prat, have reported experiences with it. I personally have performed it 37 times.<sup>3</sup> The moment seems to have come to indicate briefly the essential facts which the procedure has taught me. Elaborating the idea of Jaboulay, we must indeed develop a true and general operative method susceptible of very varied applications.

I think at the outset that it ought to be designated by an exact name: it is a peripheral sympathectomy which, according to the level where it is practised, ought to be called axillary sympathectomy, brachial, iliac, femoral, etc.

I. TECHNIQUE.—In order to achieve it, it is necessary to uncover the artery by the classic procedure, open with the bistoury the cellular sheath, separate the artery for 8 to 10 cm., get hold of the inner sheath directly on the vessel wall, incise it, pull one of the lips thus made with a forceps, free it either with the bistoury or with the grooved probe, completely stripping the artery of all the cellular tissue that adheres to it. More or less easily according to the cases, one is able thus to strip the artery, to decorticate a fold; thin, to be sure, but often thicker than one might expect. At a certain moment one has the impression that one is going to tear the wall of the artery; but if one proceeds gently and carefully, guided by the point of the bistoury or probe, the freeing process can be carried on without risk of injuring the vessel. Only twice have I had the annoyance of making a small tear in the artery; the accident was without serious results. In case of necessity one would frankly resect the segment of the tear and tie the two ends, accomplishing thus by the same act a complete sympathectomy. Sometimes the forceps removes only rather short cellular fragments, at other times one removes quite definite laminae, and the movement of freeing recalls, on a small scale, the subserous decortication of an inflamed appendix, but one never succeeds in removing a continuous layer; it is necessary to repeat the attempt several times and with perseverance to catch the sheath again, to remove thin meshes, and not to stop until one has really the feeling of having removed everything. Moreover, one can verify what has been done by wetting the wound with a tampon soaked with very warm serum: the artery takes on then a whitish appearance, looks as though made of felt, and one sees very clearly whether there remains still some cellular débris more or less detached.

In the course of the cellular decortication it is necessary to be careful to expose the collateral branches and guard against tearing them. This happens sometimes; by using then a forceps and a ligature of 00 catgut one repairs this accident without injury to the artery. In addition to the tears, which cause a spurt of pure blood, there may be oozing from the tearing of the vasa vasorum.

II. THE PHYSIOLOGICAL REACTION.—The operation thus done is a physiological operation; I mean to say by this that it is inevitably followed by a characteristic physiological reaction, which may be regarded as the *test of the operation*; as there are characteristic signs of the section of the trunk of the sympathetic in the neck, so there are characteristic signs of the section of the periarterial sympathetic nerves. If these are wanting, the operation has been attempted but not accomplished.

The results of our studies of these signs Heitz and I have reported to the Société de Biologie;<sup>4</sup> they are as follows:

*Primary Sign.*—When one touches the sympathetic sheath, the

<sup>3</sup> More exactly, I have done 30 sympathectomies by denudation and 7 times complete sympathectomy by resection of a segment of obliterated artery.

<sup>4</sup> Leriche and Heitz: Des effets physiologiques de la sympathectomie périphérique (réaction thermique et hypertension locales). C. R. de la Soc. de Biol., 20 Janvier, 1917.

artery contracts; it is reduced progressively in size to the point where it is not more than a third or even a fourth the normal size throughout the whole extent of the denuded segment. The segments on both sides maintain their normal size provided the operation has not injured them. The phenomenon is more or less rapid according to the case; certain individuals appear to have more irritable sympathetic nerves than others; their arteries diminish in size at the first touch; with some the contraction is sluggish. One cannot yet give the real reason for these variations. Furthermore, the contraction is more marked in the brachial than in the axillary and the subclavian; it is slower in the femoral than in the brachial, and less intense in the common iliac than in the femoral. In a word, the contraction is stronger in the arteries of small size than in the large trunks.

This arterial contraction habitually causes the pulse to disappear, but it does not altogether interrupt the circulation.

*Secondary Signs.*—In the following hours the pulse is imperceptible or very feeble and the limb is colder than the other. Then little by little, at the end of three hours, six hours, and most often after twelve or fifteen hours there appears the characteristic physiological reaction, the establishing of which ought to be exacted as proof that suppression of the sympathetic nerves has been properly done.

This reaction is characterized by an elevation of the local temperature reaching to  $2^{\circ}$  and even  $3^{\circ}$  [centigrade], by the elevation of the arterial pressure, and by the augmentation in the amplitude of the oscillations of Pachon. M. Heitz, who with his very special competence has established these facts many times on my patients, has found that the increase in pressure could be as much as 4 cm. of mercury in comparison with the healthy side (method of Riva Rocci); it is a detail worthy of mention that analogous figures were noted by Claude Bernard in his investigations of the cervical sympathetic nerves.

This vasodilator reaction is only temporary: the hyperthermia, the rise in pressure, and the increase in amplitude of the oscillations diminish little by little; sometimes as early as the 15th day and usually at the end of month one finds it no more. On the other hand, in some cases in which I have performed sympathectomy on the brachial or the subclavian artery by resecting totally the obliterated arterial cord, the elevations of temperature have been more lasting than in the cases in which a sympathectomy by denudation alone was done. This is comprehensible, for the operation is more complete—the sympathectomy being necessarily total. Classed with these observations should be one made by M. Babinski and M. Heitz: four months after the extirpation of an axillary aneurism the hand on the side operated on was frequently warmer than that on the healthy side. This phenomenon, apparently paradoxical, is understood very well when one considers that the ablation of a sac is in reality a total sympathectomy.

III. THE LESSONS FURNISHED BY THE OPERATION.—Observation of series of operations and analysis of the therapeutic results permit interesting deductions from physiological and pathological points of view.

1. *From the Physiological Point of View.*—Two facts become clear: the vasomotor phenomena which Heitz and I have studied under the name of vasodilator reaction permit us to isolate the paths along which certain vasoconstrictive acts are conducted and to establish their correct value.

But there is, above all, this one: it seems to follow from certain observations that the voluntary muscular contraction is, in a certain sense, very dependent on the sympathetic nerves. The integrity of the motor nerve and of the muscle are not sufficient to insure the proper accomplishment of the movement that is commanded. If the sympathetic nerve is affected at a distance or if it does not act normally, the muscle becomes hard, and contracts, and the will is powerless to relax or contract it. Now in these cases sympathectomy lifts the barrier and makes possible

the progressive reparation of the voluntary movements. In the case of wounded men having reflex contractions of the Babinski-Froment type, with fingers twisted, motionless, incapable of movement, it has been sufficient to modify the vasomotor innervation to see a certain degree of voluntary motion appear again the following day.

This fact which M. Heitz<sup>a</sup> and I have confirmed several times has a real physiological bearing. What we now know of muscle innervation in man does not lead us to suppose that it is a matter of a directly muscular action. It appears, until we have made further inquiry, that the vasomotor phenomena alone are concerned in it, and a fact which would tend to prove this is that the return of motility coincides with the appearance of the post-operative vasodilator reaction (that is to say, the warming up of the muscle, its new circulatory system), and follows the course of it.

Sympathectomy, furthermore, would appear to establish the fact that the sympathetic nerve is, in man, the excitosecretory nerve of the sweat glands; I have seen profuse sweating of the hand disappear after sympathectomy. The nerve probably also influences the growth of the nails and the trophicity of the skin, since trophic phenomena disappear rapidly after sympathectomy. The nerves of the cerebrospinal system, from this point of view, are probably only the vectors of the sympathetic.

2. *From the Point of View of Pathological Physiology.*—Sympathectomy is, in certain cases, a true method of experimental analysis for the interpretation of certain complex phenomena.

It demonstrates: (a) *The true mechanism of the production of dry wounds of the arteries.* Spontaneous hemostasis, when an artery is divided or destroyed by a projectile, is certainly greatly facilitated by, if it is not entirely due to, the contraction of the artery which follows the destruction of its sympathetic nerve. It may be compared to the considerable diminution of calibre which is observed after sympathectomy. Since a brachial artery is reduced to the size of a radio-palmar or a digital when its sympathetic nerve is excised, it is easy to comprehend how spontaneous hemostasis is possible after certain wounds of the arteries which are inevitably accompanied by tearing of the sheath.

(b) *The real nature of certain causalgias, if not of all.* As I demonstrated to the Société de Neurologie, in January, 1916, one can cure obstinate causalgias by excising the involved sympathetic nerve. This observation proves the sympathetic origin of the violent pains which accompany certain wounds of nerves. In these cases the pain phenomena are not due to the nerve lesions, but to the lesions of the neighboring sympathetic nerve (the perivascular sympathetic of the brachial) or of the intra-nerve sympathetic (the sympathetic carried to the median, for example, by its particular artery). This explains the fact demonstrated by M. Pierre Marie, M. Miege and Mme. Bénisty that the pain in these nerve wounds is a kind of reaction peculiar to the nerves which have an artery of their own or which are close to a large artery. This fact is now admitted by the neurologists.

(c) *The very great rôle of the sympathetic in the production of the reflex contractions of Babinski-Froment.* Let us pay attention to the characteristics of this type about which there is so much confusion. I speak now of the true Babinski-Froment type, that in which the vasomotor and thermic phenomena are associated with motor disturbances and with modifications of the mechanical excitability of the muscles.

In the cases of this kind, studied by M. Babinski or by his assistants Froment and Heitz, I have seen with Heitz motor disturbances disappear almost completely after sympathectomy. From the day following the operation, when the vasodilator

<sup>a</sup>Leriche and Heitz: Influence de la sympathectomie péri-artérielle ou de la résection d'un segment artériel oblitéré sur la contraction volontaire des muscles. Société de Biologie, 17 Février, 1917.

reaction was very well established, the mobility returned markedly in hands fixed immutably in position, contracted, the fingers being bent into the palms, or else turned back on the dorsal side. I am inclined to believe that a number of these severe cases are referable to disturbances of sympathetic origin, caused by the imprisonment of the nerve ends in a hard and compressing cicatrix.

(d) *The rôle of the sympathetic in the production of certain griffes cubitales.* After brachial sympathectomy I have seen a loosening up of a very rigid *griffe cubitale* which had resisted resection and suture of the nerve divided in the forearm.

I have made this observation only once, but the phenomenon was perfectly definite. It seems to me that the observation should be recorded because of its therapeutic interest.

(e) *The rôle of the sympathetic in the explanation of those motor paralyses, more or less complete, which follow certain arterial lesions,* when the nerves have not been disturbed. We call it ischemic paralysis, giving to this appellation an entirely different sense from that which we have in mind for the isolated contracture of the flexors of Volkmann. In the cases described by MM. Déjerine and Tinel there is rather complete motor paralysis with the reaction of degeneration, yet the nerves were not divided. The paralysis coincides with an edematous infiltration of the hand with marked vasomotor disturbances which lead to true fibrous transformation of the hand. At the end of some weeks the edema begins to diminish, the tendons and the aponeuroses are ensheathed in a veritable fibrous envelope; the muscles, already hard and tense, retract and take on a ligneous consistency. In this picture is seen the mark of the sympathetic; and in doing sympathectomy in these cases M. Heitz and I have seen vasomotor disturbances disappear, trophic disturbances improve, the tendons and the muscles become on palpation sensibly more supple, and the muscles execute slight movements. In one case, although before operation there had been complete degenerative reaction, four months after operation we observed a very definite amelioration of the electric reactions, and we are hoping for a marked functional recuperation.

I do not wish to say that sympathectomy cures the patients; and it is impossible that it should cure them at once when one considers their wounds. Unhappily, there is no cure, but to me it appears to have caused the disappearance (at least momentarily) of the stiffness of the muscles and tendons; it has assured a manifest suppling up of muscles which, after the sympathectomy, executed movements equivalent to one half the normal. Referring to the fact mentioned above à propos of *griffe cubitale*, I have the impression that the sympathetic has an enormous influence on the evolution and production of fibrous tissue. The sclerous evolution is modified, it appears, when a vasodilator reaction is brought about. Whence the conclusion that the sympathetic plays probably a large rôle in the mechanism of the so-called ischemic paralyses where the predominating feature has not the mark of ischemia. I do not mean to say that the circulatory suppression caused by the arterial lesion does not play any part, that would be absurd; what I would say is that something more is involved. But these cases are too rare in general surgical practice for me to follow the analysis alone.

(f) *The rôle of the sympathetic in the production of heel sloughs in the course of medullary lesions.* In one patient who had had flabby incomplete paralysis of the lower limbs with absence of reflexes, and incontinence of urine, there were two sloughs, one on the heel, the other on the little toe. They resisted all treatment. Three months after the wound had been received, a femoral sympathectomy was done. Three days later the ulceration of the toe was dry and cicatrized; that of the heel, which was as large as a small palm of the hand, diminished in size and was covered with active granulations. In thirty-five days it was completely cicatrized.

3. *From the Therapeutic Point of View.*—I have tried sympathectomy in a great variety of cases, and it is rather difficult for me to analyse the results, because there were often complex situations to be dealt with. Schematically, I have tried to influence the element of pain, the element of reflex contraction with vasomotor disturbances, and the trophic element. In all the cases I have had failures and disappointments.

I have done sympathectomy eleven times for phenomena of pain; once the vasodilator reaction failed. This operation was badly done and I eliminated it. For the ten others, six times there were true causalgias, and three times phenomena of pain more or less intense.

For *causalgia* I operated four times on the upper extremity, twice on the lower limb. The four cases in the upper extremity resulted as follows: One complete failure (patient operated on in the service of M. Gosset), two excellent results (complete suppression of the pains, total transformation of the patients) with final cure, now dating back 19 and 16 months. These two patients have been discharged, and are earning their living exclusively by their own work.

In a fourth case, which was very serious, I had found the brachial artery obliterated. I had not at the time thought that there would be any advantage in resecting the obliterated segment. I performed then a sympathectomy by denudation. The patient was much improved; he who for months had been confined to his bed with a wet cloth on his hand, apprehensive, indifferent to everything except his pain, got up and submitted to the same régime as his comrades; but some pains persisted. In order to improve these I again took the patient under my care and resected the obliterated arterial segment, whereupon the persisting disturbances almost completely vanished; this result promises to be permanent.\*

In the lower limb I did one femoral sympathectomy, with appreciable amelioration. At a second operation I resected the sciatic artery and the artery of the sciatic nerve, with manifest result, but the cure has not been complete. The patient, who has been followed for six months, is entirely relieved at certain times, but has suffered much at others in damp weather. His general condition is transformed. For those who know the lamentable condition of degeneration of these patients caused by their martyrdom of pain, the words "great amelioration" have a real significance. This expression should not be taken as a euphemism masking a failure.

In another case I did a common iliac sympathectomy, which resulted in great improvement [grande amélioration] with complete transformation of the general condition. The patient has suffered at certain times, but his days of respite have been greater in number than his days of pain. This is also, to my thinking, a success worth trying for.

For all "causalgiques" the question is complex in other ways: these patients have a psychology of their own; it is necessary to isolate them somewhat and to exercise over them a little authority if we desire to cure them. Besides, they are extremely sensitive to atmospheric changes, and it seems as if their whole vasomotor system were out of equilibrium. One local operation could not pretend to set all this right at once, and these patients should not be regarded exactly as others.

I have operated four times for phenomena of pain accompanying nerve lesions or arterial obliterations. I had three excellent results and one complete failure.

To sum up, in the treatment of the phenomena of pain, sympathectomy cures entirely certain patients, acts very favorably in the majority of cases, but does not succeed always or always give an absolutely perfect result.

\*In one of the last Bulletins of the Société de Chirurgie a very interesting observation by M. Le Jemtel is reported, which shows well the rôle of the sympathetic in the paretic syndrome following an obliteration of the brachial.

Five sympathectomies for *trophic ulcerations*, with or without phlyctenæ in the neighborhood, gave success five times.

I have operated three times for large bluish ademas of the limbs, with one complete success; one great improvement, followed at the end of several months by complete cure; one incomplete result with partial return (in the lower limb), but on the whole, amelioration.

For *reflex disturbances*, eighteen sympathectomies among the patients examined heretofore (except two) either by M. Babinski, or by his assistants M. Froment and M. Heitz, and all followed up by M. Heitz, have resulted as follows:

Three cures, practically complete, traced for several months, with disappearance of the vasomotor disturbances and of the contraction;

Ten ameliorations more or less considerable, some of which were almost cures;

Two ameliorations followed by incomplete return in patients who had not received any post-operative treatment. In the two cases the lasting benefit has been real;

One case in which the operation, after failure of all other treatments, has been followed by the execution of voluntary movements; also, thanks to treatment followed regularly under the direction of M. Heitz, motility is returning little by little;

Two complete failures. In these two patients there had been after operation a beginning return of voluntary motility, but the therapeutic result has been practically nil.

In all the patients who have been really benefited by the operation (16) the vasodilator reaction has been followed by a diminution of the contraction and by a reappearance more or less complete of the voluntary movements. In some cases the result has been surprising: from the day following operation the patients were able to make movements which had been impossible for months. But at the end of two or three weeks, as the vasodilator reaction subsided, the contraction shows signs of beginning anew and the movements diminish in amplitude. Observing this, we thought, with M. Heitz, that the maintenance of heat in the member operated upon was indicated. For this purpose M. Heitz has made my patients take baths of paraffine at 60° for about one half hour. By associating with this treatment massage and reeducation Heitz has obtained very interesting results, which permit us to speak, in certain cases, of true cure.

<sup>1</sup>The observations will be published *in extenso* in the August number of Lyon chirurgical, under the following title: Résultats de la sympathectomie péri-artérielle dans le traitement des troubles nerveux post-traumatiques d'ordre réflexe.

Briefly then, in the grave forms of the syndrome of Babinski-Froment sympathectomy by itself does not suffice. But without it, the treatment usually applied soon ceases to influence the condition, and the result becomes stabilized; the operation, like so many other operations upon the nervous system, leaves room for and facilitates reeducation, and gives to it its efficacy. It is only one phase of the treatment, but it is a very rewarding phase. I insist on this point so that we shall not expose ourselves to failures all the more bitter when the operation at the outset promised to yield a brilliant result. And I recall what Heitz has recently written:<sup>2</sup> it is the mixed method (operation on the sympathetic followed by the treatment indicated above) which has given in the service of M. Babinski the best results.

For the paralyses connected with vascular obliterations, associated or not with nerve lesions, sympathectomies have improved the condition without giving, except in one case, a true functional result. In such case the sympathectomy should be done to modify the vascularization of the paralyzed segment, to check the fibrous regression of the muscles. It cannot constitute of itself a sufficient treatment, but it has appeared to me to be interesting and useful. The future will determine its indication.

It is the same in regard to the value of sympathectomy associated with operations upon the nerves in cases of rebellious contracture of the median or of the ulnar nerve variety. One cannot say definitely, but the question appears to me to merit consideration.<sup>3</sup>

In order to estimate the results of sympathectomy I have striven to be as concrete as possible: I have appraised as nil any result which was without value for the patient. The verdict may perhaps appear to be very reserved. Truly, I believe that the operation is a very interesting one and a useful expedient to which one may resort in cases, very diverse, which have been irresponsive to all other treatments; but it remains for us to define clearly the indications for it.

<sup>2</sup> Heitz: Des troubles circulatoires qui accompagnent les paralysies ou les contractures post-traumatiques d'ordre réflexe. Archives des maladies du cœur, Avril 1917, p. 160.

<sup>3</sup> Recently I tried to arrest, by sympathectomy, the appearance of gangrene after resection of the popliteal vessels. The operation was followed by complete disappearance of the pains; it changed the hue of the violet-colored spots which covered the limb. For 36 hours I hoped for a therapeutic result, but none appeared, and I had to amputate the thigh.

## PUBLICATIONS

The following nine monographs:

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

Leukaemia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D. Price, \$2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICHT and T. WINGATE TODD. Price, \$2.00.

The Operative Story of Goitre. The Author's Operation. By WILLIAM S. HALSTED, M. D. Price, \$3.50.

Study of Arterio-Venous Fistula with an Analysis of 447 Cases. By CURLE L. CALLANDER, M. D. Price \$2.50.

Other monographs will appear from time to time

# BACILLARY DYSENTERY IN CHILDREN

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## SUMMARY

**Introduction.**

**Source of Material.**

**Clinical Data.**

**Etiology (Bacteriological and Serological Data).**

Dysentery Cases.

Control Series (63 cases of simple non-infectious diarrhoea and 100 normal children).

**Epidemiology and Prevention.**

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**Appendix (Bacteriological and Serological Technique).**

## INTRODUCTION

Bacillary dysentery is a disease chiefly affecting babes and soldiers.\* In the former it sometimes masquerades under the names of summer diarrhoea, infectious diarrhoea, colitis or ileocolitis, which do not have the prestige and importance that is attached to the more ominous title "dysentery." That this disease in children is caused by *B. dysenteriae* has long been known,<sup>1, 2, 3, 4, 5, 6</sup> and is adequately confirmed by the bacteriological findings in our series of cases. The name "summer diarrhoea" is particularly misleading. One might as well discuss "winter cough" as was done in 1872<sup>7</sup> and neglect to differentiate primary and secondary pneumonia from bronchitis. There are many types of intestinal disease that occur during the warm months and there is no reason for classing them all together, for dysentery stands out sharply on clinical as well as bacteriological grounds.

## SOURCE OF THE MATERIAL

The material for this report consisted of the study of 134 cases of diarrhoea. Eighty of these were in the wards of this hospital from March, 1919, to February, 1920, nine cases in the Thomas Wilson Sanitarium, Mt. Wilson, Maryland, during June and July, 1919, and 45 cases in the private practices of several physicians in Birmingham, Alabama, from July 14 to August 9, 1919.†

\* The results of an investigation of an epidemic of bacillary dysentery in our troops in France (A. E. F.) will appear in a later article.

† These latter cases were studied by Dr. Harold L. Higgins and myself at the request of Dr. John Howland and with a grant of money from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association. Through the courtesy of Dr. J. D. Dowling, Health Officer of Birmingham, Alabama, and Dr. J. R. Bean, we were given all the facilities in the Board of Health Laboratory. Through the efforts of Drs. Thomas D. Parke, Russell Callen, Courtney W. Shropshire and 15 other physicians, we were able to obtain stool specimens from several cases of diarrhoea in infants in Birmingham and its environs. Our sincere thanks are due these physicians and also Drs. Catherine Creighton, Harold L. Higgins, L. V. Rosenthal and C. E. Wagner for assistance with the bacteriological work.

## CLINICAL DATA

Among the total 134 cases of diarrhoea, 71 were diagnosed by the clinicians as cases of dysentery (ileocolitis).

Clinically, the disease is a definite type, occurring usually in well-nourished and previously healthy children whose ages ranged from 3 months to 11 years (see Table I). The

TABLE I.—AGES OF BALTIMORE AND BIRMINGHAM DYSENTERY CASES

	Ages of all Baltimore dysentery cases	Ages of all Birmingham cases	Ages of fatal Baltimore cases	Ages of fatal Birmingham cases
Average .....	16 months.	25½ months.	11 months.	15 months.
Mean (excluding wide extremes)	14 months.	17 months.	5½ months.	12 months.
Minimum.....	3 months.	6 months.	4 months.	6 months.
Maximum .....	36 months.	182 months (11 years).	36 months.	30 months.

ages of the Birmingham patients were higher than those of Baltimore. This may possibly be explained by the fact that in the former breast feeding was a more general rule and therefore the younger children escaped infection.

With one or two doubtful exceptions, none of the patients was exclusively breast fed, but received supplementary feedings of whole milk, proprietary foods or general diet.

The onset was usually characteristic and sudden (see Table II). The child lost his appetite and showed evidence

TABLE II.—CHARACTER OF ONSET OF BALTIMORE DYSENTERY CASES \*

No. of cases	Sudden onset with fever	Inidious onset	Dysenteric infection occurring during course of other disease	Vomiting at onset	Irritability and nervous symptoms at onset	Convulsions at onset	Loss of appetite and refusal of food at onset	Previous intestinal disease (several months prior to dysenteric infection)	Average time of appearance of blood in stool after onset
23	23	4	2 cases, (lost + o-myelitis, tarsury).	14	14	6	10	3	2.3 days.
Percentage	79	14	7	52	48	21	84	10	

\* Analysis based on 29 cases in which the histories were complete.

of having fever. Irritability, vomiting and convulsions were frequent initial symptoms. Within a few hours there was an increase in the number of stools. These were at first fecal, rarely green, becoming blood-tinged on the second day, and within four days consisted almost entirely of blood and mucus. The number of stools ranged from 3 to 30 a day. The size of the stool was usually small and seemingly out of proportion to the patient's straining efforts.

The fever subsided in most cases by the fifth day. The patients were usually quite ill, crying feebly when disturbed, were drowsy and apathetic, after their initial irritability had ceased, and had little or no appetite. Loss of sleep due to the frequent and often painful bowel movements was a distressing factor. Dehydration and marked loss of weight was evident by the end of the first week.

In the patients that recovered, the blood disappeared from the stools during the second week and the diarrhoea abated by the 14th day.

Such was the course in 79 per cent of our cases. In 14 per cent (4 cases), however, the picture was misleading. With these four children, there was no sudden onset. They had been under observation for over one month with symptoms of intestinal indigestion; *i. e.*, occasional vomiting and from three to six loose green stools a day which frequently contained mucus. Their weight was stationary or showed slight losses and they were malnourished. After several weeks of these symptoms, the stools became blood-tinged and were increased in frequency to nine or eleven a day. The temperature was slightly increased. This picture remained unchanged for several days and then the condition returned to the former state of mild diarrhoea. During the period of bloody diarrhoea *B. dysenteriae* (Flexner) was isolated from the stools of three of these four cases and agglutinins for *B. shigæ* were demonstrated in the serum of the fourth. Were these four cases instances of chronic dysentery that had become worse or did the bloody diarrhoea represent a dysenteric infection that had become superimposed on a previously inflamed intestinal mucosa? The latter appears to be the more probable explanation.<sup>7</sup>

Such cases must be distinguished from cases of intestinal indigestion in which the stools contain streaks of blood (usually bright blood) for only one or two movements and never longer than one day. This blood is probably the result of mechanical irritation of the lower rectum due to straining. The cultural results in such cases were negative.

In two other patients there were histories of intestinal indigestion several months previously, from which they had completely recovered. There were no agglutinins for *B. dysenteriae* in the serum of the only one that was tested during this earlier period; yet when he came into the hospital four months later with clinical dysentery, the reaction was positive, so that it would seem probable that the previous diarrhoea had no connection with the later dysenteric infection.

However, it must not be forgotten that in adults a mild non-bloody diarrhoea lasting only 24 hours has been proven to be due to dysenteric infection.<sup>8</sup> There is no reason to suppose that similar cases cannot arise in children.

In two other cases (seven per cent) the diagnosis of dysentery was marked by the presence of other diseases; in one by scurvy (proven by X-ray) and the other by osteomyelitis. *B. dysenteriae* (Flexner) was isolated from the stools of each of these cases.

In the dysentery cases in Baltimore and Birmingham there were 67 white children with 14 deaths and 4 colored with 1 death, a total mortality of 21 per cent.\*

An analysis of the ages of the fatal cases in Table I would seem to indicate that the younger patients were more vulnerable.

The leucocyte count of the Baltimore cases was slightly increased.<sup>9</sup> The mean was 13,000 for all cases and 13,700 for those that died. Wide variations, without obvious cause such as otitis media, were, however, to be noted. In fact the leucocyte count was of little or no diagnostic importance.<sup>10</sup>

The physical findings were of little assistance. In only one case was the spleen palpable. The liver was occasionally somewhat enlarged and tender. Abdominal tenderness was not marked. Five of the patients were emaciated on admission and two had obvious rickets.

Complications were infrequent.<sup>11</sup> Pyelitis occurred in one case, *B. coli communis* being isolated from the catheterized urine. Otitis media developed in two cases. Hyperpnœa<sup>12</sup> occurred in three cases.

It is frequently stated that after recovery from dysentery (ileocolitis) the feeding of the small patients may become a difficult problem. This has occurred in very few of our cases. Occasionally there was persistent refusal to take food so that gavage was necessary for a few days. With these exceptions, all of the other patients took their feedings well and showed a steady increase in weight; after three months they were well-nourished, exceedingly healthy children. No case became chronic.

Clinically (as well as bacteriologically) there was no difference between the cases we saw in Birmingham and those that we have studied in Baltimore. However, the ratio of dysentery (ileocolitis) cases to those of simple non-infectious diarrhoea was 8 to 1 in Birmingham and 1 to 2 in Baltimore.

The post-mortem diagnoses in practically all of the children that died of uncomplicated dysentery were definite diphteritic or ulcerative or acute necrotizing enterocolitis depending on the nomenclature of each pathologist. In fatal cases in children suffering from malnutrition, scurvy, rickets or other diseases in which dysentery had acted as the last straw, as a complicating and not the primary cause of death, the post-mortem diagnoses of the intestines ranged from normal to hyperemia or slight ulceration of the lymph follicles of the lower third of the ileum and the colon. In other words, the autopsy revealed the severity of the infection and the virulence of the causative organism. It is frequently stated that the degree of ulceration of the intestine depends upon the length of the illness. This statement did not appear to be true in this series of cases.

The autopsy of one case of Flexner dysentery of but three days' duration showed the ulcers and membrane formation of typical acute enterocolitis.

\* The mortality for these 1919 cases was lower than that of former years, for among 114 cases treated at the Harriet Lane Home from 1912 to 1918 inclusive, there were 33 deaths, a mortality of 29 per cent.

Three days after the death of this patient, his brother developed clinical dysentery which cleared up after an illness of two weeks. *B. dysenteriae* (Flexner) was isolated in this case also.

Similar findings occurred in the remaining uncomplicated fatal dysentery cases. Occasionally in addition to the ulceration of the lower third of the ileum and the colon, there were evidences of fatty degeneration of the liver. These probably correspond to the findings reported by Parke in cases in Birmingham.<sup>23</sup>

#### Etiology—BACTERIOLOGICAL AND SEROLOGICAL DATA

##### DYSENTERY CASES

In Birmingham, Alabama, from July 14 to August 9, 1919, I cultured one or more specimens of the stools of 40 patients with clinical dysentery. Only half of these were in the acute stage of the disease and from only 13 did we obtain satisfactory specimens because all of the patients except two were in private homes scattered throughout the city and it was often impossible for us to be notified until the stool specimen had become too old to give reliable bacteriological results.

Of the 13 cases from which we received satisfactory stool specimens, I recovered *B. dysenteriae* (Flexner) \* in six cases, *B. dysenteriae* (Shiga) in one and *B. dysenteriae* (Kruse E)<sup>24, 25</sup> (or *B. dispar*)<sup>26</sup> in one. (A description of the technique employed is appended.) Positive agglutinins for *B. dysenteriae* (Shiga) were demonstrated in the sera of two additional patients. (The latter were brother and sister in a family in which one child had died the week previously of clinical dysentery and both parents were convalescent from dysentery.) In other words, in these thirteen cases, infection with *B. dysenteriae* was demonstrated in ten.

Of the 31 cases of clinical dysentery in the wards of this hospital, *B. dysenteriae* (Flexner) was recovered in eighteen. Positive agglutinins for *B. dysenteriae* (Flexner) were demonstrated in seven additional cases and for *B. dysenteriae* (Shiga) in one further case. Three were negative culturally but agglutination reactions were not done and two were negative bacteriologically and serologically. In other words, infection with *B. dysenteriae* was shown in over 83 per cent of the cases of clinical dysentery in the Harriet Lane Home during the past year.

The ratio of Flexner to Shiga infections was 8 to 1. The Flexner bacillus is usually the more common type in children.<sup>27, 28, 29, 30</sup> In fact, some investigators<sup>29, 30</sup> found mixed infections with both varieties more frequently than the Shiga type alone.

The dysentery agglutination reaction assists the diagnosis of dysentery.<sup>31, 32</sup> It is essential, however, for each worker to standardize his cultures and technique with normal control sera, especially in Flexner infections, inasmuch as the agglutinability of different strains of this organism varies considerably. Freshly isolated strains should not be used, for

their agglutinability is inconstant. I have used the standard agglutinable cultures issued by the Department of Pathology, University of Oxford, on behalf of the Medical Research Committee (England) and also formalized cultures made according to Prof. Georges Dreyer's<sup>33</sup> instructions and found (Table III), as he states, that macroscopic dysentery ag-

TABLE III

Case no.	Age at onset	Agglutination reactions of the patient's serum			Type of dysentery bacillus isolated from stool culture
		Days after onset	Flexner culture	Shiga culture	
23	7 months.	2 4 9	? 1/25 ± 1/25 + 1/50	0 1/25 0 1/25 0 1/20	
82	5 months.	6	± 1/200	+ 1/50	
58	4 months.	10	0 1/20	0 1/20	Flexner (inagglutinable).
11	24 months.	7	+ 1/500	0 1/25	Flexner.
10	15 months.	9	+ 1/200	Not done.	Flexner.
16	36 months.	9 15	+ 1/100 + 1/250	0 1/20 + 1/50	
78	11 months.	13	+ 1/20	Not done.	Flexner.
54	30 months.	14	+ 1/100	0 1/20	Flexner.
79	9½ months.	17 21	+ 1/200 + 1/100	0 1/20 0 1/20	Flexner.
80	26½ months.	19 33	+ 1/200 + 1/200	0 1/20 0 1/20	Flexner (urine culture).
46	36 months.	21	+ 1/1000	0 1/20	Flexner.
8	19 months.	13½ before onset. 21 after onset. 158 after onset.	0 1/25 + 1/50 + 1/20	0 1/25 0 1/20 0 1/20	
77	8 months.	26 76	± 1/50 + 1/50	0 1/20 0 1/20	Flexner.
42	22 months.	27	+ 1/100	0 1/20	
44	23 months.	37	± 1/20	0 1/20	
50	3½ months.	38 140	0 1/20 0 1/20	0 1/20 0 1/20	
59	14½ months.	39 138	+ 1/100 ± 1/50	0 1/20 0 1/20	
63	6½ months.	68 172	+ 1/20 0 1/20	0 1/20 0 1/20	Flexner.
56	3 months.	90	+ 1/20	0 1/20	Flexner.
45	17 months.	176	0 1/20	0 1/20	Flexner.
41	14 months.	184	± 1/20	0 1/20	Flexner.
39	23½ months.	200	± 1/50	0 1/20	Flexner.
40	11 months.	205	± 1/200	0 1/20	Flexner.
2	48 months (4 years).	18	0 1/25	± 1/50	
4	132 months (11 years).	20	0 1/25	+ 1/125	
37	14½ months.	45	0 1/20	+ 1/50	

Five Flexner antigens (cultures) English (Murray) types V, W, X, Y and Z were used for agglutination, and the reactions denote the highest titres for any one of them. All of these patients had clinical dysentery.

glutination by a patient's serum with standard agglutinable cultures or comparable preparations in a dilution 1:30 (6-8 units) is suggestive and a titre of 1:50 (10 or more units) is diagnostic of previous or present dysentery infection.\*

\* In infants and young children a positive dysentery agglutination even at a dilution of 1:20 early in the disease is very suggestive. In my experience non-specific agglutination in young children is infrequent.

\* By *B. dysenteriae* (Flexner) I refer to the whole group of manite fermenting dysentery bacilli.

In all patients from whom an agglutinable *B. dysenteriae* was recovered and whose sera were tested, specific agglutinins were found. In only three patients who were not, at that time, suffering from bloody diarrhoea did I demonstrate dysentery agglutinins (*vide infra*).

The literature on this subject is contradictory. It is frequently stated that the patient's serum reactions in dysentery are worthless.<sup>15</sup> It is just as frequently claimed that they are infallible. Glynn and his co-workers<sup>16</sup> give an excellent analysis of the various methods and insist that agglutination, if done with standardized methods, is reliable.

The confusion on this question is readily explained. If a freshly isolated living culture of *B. dysenteriae* is used for agglutination, a positive result may be obtained with a known serum in a dilution of 1:500. A few weeks later the same serum and a subculture of the same *B. dysenteriae* strain may give a positive agglutination at an end titre of only 1:100. In other instances a freshly isolated *B. dysenteriae* culture may be agglutinated only at the end titre of 1:100. Yet after a few weeks of laboratory cultivation, positive agglutination may be noted with the same serum at a titre of 1:500.

Obviously, then, if a laboratory worker tests the sera of normal persons with either of these two types of culture, his figures are useless for later comparison with the agglutination results of patients with dysentery.

If living cultures of older laboratory strains are used, this difficulty may be remedied though not cured, for although strains that have been artificially cultivated for long periods have reached quite a constant level of agglutination, yet there is still some variation. Furthermore, the emulsions of these living cultures will vary in opacity and thickness from day to day. This will also give confusing results for agglutinations with the same serum, and emulsions of the same strain which are of different opacity will give different end titres. Thinner emulsions, within certain limits, will be agglutinated by the same serum in higher dilutions than those that are more opaque.<sup>20</sup>

These are some of the arguments Dreyer, Ainley, Walker, Gibson and others<sup>21, 22, 23</sup> have advanced in support of the Oxford Standard agglutinable cultures. It is not to be denied that conflicting results have been obtained by some investigators<sup>24</sup> with Dreyer's method. In the main, however, they have been most satisfactory and results in different laboratories are thus comparable.

Furthermore, it is not as clearly recognized as it should be that while there is but one type of Shiga dysentery bacillus, there are at least five subdivisions of the mannite-fermenting group. Murray<sup>25</sup> has designated these as *B. dysenteriae* (Flexner) types V, W, X, Y and Z (based on agglutination) and has dropped the older subgroup names of Flexner, Harris, Hiss-Russel-Y and Strong (based on the differences in fermentation of maltose and saccharose). If agglutination reactions with patients' sera are done with only one or two types of the Flexner bacillus as antigens, obviously some positive tests may be missed.<sup>26</sup>

I have studied 89 cultures \* of mannite-fermenting dysentery bacilli isolated from these cases and was able to differentiate them culturally into seven divisions on the basis of the fermentation of maltose, saccharose, dulcite and rhamnose. These cultures were also differentiated serologically by their agglutination reactions with Murray's five (English) Flexner monovalent rabbit sera, types V, W, X, Y and Z. These serological divisions did not run parallel with the fermentative divisions. A general correspondence existed between the serological types of the organisms isolated from the patient's stool and agglutination reactions of his serum. One or the other and not both of these methods of division must be adopted. The classification by agglutination is advisable, because it is simpler and more rapid. The results of the agglutination reactions of the patient's serum may be expressed in the same terms as the serological typing of the organisms from his stool. Fermentation is less constant and gives rise to more divisions than there are carbohydrates.

The serological reactions of these type sera, as Murray states, show cross-agglutination to a greater or less extent but they indicate that there are five antigens V, W, X, Y, Z and probably others, one or more of which predominates in a given strain. Polyclonal diagnostic and therapeutic dysentery sera are practically worthless unless they include antibodies for the more common of these types.

In the agglutination reactions recorded in this paper, eight dysentery antigens were used, *i. e.*, Shiga, Flexner types V, W, X, Y and Z, *B. dispar* (or Kruse E) (a lactose fermenting dysentery) and *B. ambiguum*, Schmidt<sup>27</sup> (an indol producer which forms acid and no gas in dextrose and rhamnose).

As will be seen in Table III, suggestive agglutination was noted in one case (No. 23) on the second day,<sup>28</sup> the titre rising on the fourth and ninth days. The maximum is probably on the 17th to 21st day as it is in typhoid. From the stool of one patient (No. 58) a dysentery (Flexner) bacillus, that did not agglutinate with any of the five diagnostic type sera, was isolated and this patient's blood serum had no agglutinins for the V, W, X, Y and Z stock cultures, suggesting that there are additional types in the Flexner group.<sup>29</sup> Agglutinins for both Shiga and Flexner groups were noted in only two cases.<sup>28, 29, 30</sup>

Agglutinins persisted in several cases longer than four months and in three cases tested after six months they were still present.<sup>31</sup>

#### CONTROL SERIES (63 CASES OF SIMPLE DIARRHEA † AND 100 NORMAL CHILDREN)

In addition to the 71 cases of clinical dysentery just described there were 63 patients studied who developed increased frequency of stools at one time or another during the course of other illnesses. The clinical diagnoses of these latter were

\* A paper on the "Divisions of the So-Called Flexner Group of Dysentery Bacilli" will appear later.

† The term simple or non-infectious diarrhoea or merely diarrhoea is used in contradistinction to the bloody diarrhoea of dysentery.

gastro-intestinal indigestion (47), typhoid fever (6), pyelitis (3), tuberculosis (2), hydrocephalus (1), eczema (1), bronchopneumonia (1), scurvy (1) and endocarditis (1).

The onset of the increased frequency of stools in each of these cases was insidious. There was no irritability or increased temperature. Several of the patients vomited occasionally, but loss of appetite was not obvious. Practically all gave histories of diet indiscretions especially of high sugar feeding. The stools were always fecal, usually green and contained no blood. Only in cases of long duration was mucus present in excess. In fact, in none of this group with the exception of the typhoid cases was there evidence of an acute intestinal infection.

The study of the stools of these 63 cases of simple † or non-infectious diarrhoea, as well as those of 100 normal children, serves as an admirable control series for the studies on the cases of dysentery, for in none of the former (63 cases of diarrhoea and 100 normal children) did we obtain *B. dysenteriae* from the stools. The sera of three patients among sixteen with diarrhoea tested showed positive dysentery agglutinations. Two of these gave histories of bloody diarrhoea some months before admission and, as shown in Table III, agglutinins may persist in the blood six months after a dysenteric infection. The third had typhoid fever and there is evidence to show that one infectious disease may raise the non-specific agglutinin titre.<sup>7</sup>

The negative cultural results in these cases of simple diarrhoea and in normal children when contrasted with the positive findings in 83 per cent of the cases of bloody diarrhoea indicate plainly that children presenting a symptom-complex as outlined in Table II are suffering from bacillary dysentery.

Indeed it would seem that a correct differentiation of dysentery from diarrhoea can be made in most instances on clinical data alone.

The bacteriological and serological results indicate that the Birmingham and Baltimore cases were of a similar type.

The results in Baltimore and Birmingham bear out the conclusions of Tenbroek and Norbury in Boston in 1914 and 1915<sup>8</sup> that ileocolitis in children is due to infection with dysentery bacilli. Duval and Bassett<sup>9</sup> in 1902 and the Rockefeller Commission in 1903<sup>10</sup> demonstrated *B. dysenteriae* in a high percentage of cases that they called "summer diarrhoea," but a clinical analysis of their cases shows that it was usually from the bloody and mucous stools of patients with typical dysentery that these organisms were isolated.

In fact, it would seem that ileocolitis and bacillary dysentery in children in Boston, Baltimore, Birmingham, New York and probably other cities are one and the same disease.

Some investigators have given significance to the presence of *B. welchii* (gas bacillus) in the stools of patients with diarrhoea.<sup>11</sup> They have also gone further and outlined special treatment and diets for this so-called "gas bacillus diarrhoea." However, this was soon contradicted, but although Simonds,<sup>12</sup> Knox and Ford<sup>13</sup> and others<sup>14</sup> have conclusively proven that *B. welchii* is an inhabitant of the intestines of normal chil-

dren, some paediatricians are still influenced by its presence. I have often found *B. welchii* in normal stools and am convinced that it plays no part in the etiology of clinical dysentery or non-infectious diarrhoea. Those who have studied war wounds realize that *B. welchii* does not produce dire results except in tissues where its supply of oxygen is limited. How can it be pathogenic in intestinal contents which are freely moving and well supplied with oxygen?

Perhaps the clearest analogy is found in tetanus. *B. tetani* is pathogenic in deep wounds yet it is common knowledge that this organism is frequently found in horse feces. Has any one accused the horse of "tetanus diarrhoea"?

*B. Morgan No. 1* has been asserted to be the cause of diarrhoea in children, especially in England.<sup>15, 16</sup> In this series of cases I have found this organism frequently associated in the same stools with *B. dysenteriae*. I have found it in many cases of simple diarrhoea in children and also in many adults. In no case, in which serological tests were made, did the patient's serum agglutinate *B. Morgan No. 1*. Tenbroek and Norbury<sup>17</sup> and Thjotta<sup>18</sup> report similar results. As a matter of fact the British investigators found Morgan bacilli in the stools of many normal children. In very few of their diarrhoea cases were the stools bloody and it is open to doubt whether they were dealing with cases similar to our clinical dysentery. Lewis<sup>19</sup> and Kligler<sup>20</sup> have shown that *B. Morgan No. 1* probably represents a wide group of organisms rather than a single type. I have carried out agglutination tests with four of Kligler's diagnostic rabbit sera and 50 strains of Morgan No. 1 isolated from diarrhoeal and normal stools and found that there is no uniformity in results and that many strains are inagglutinable, while others are agglutinated by more than one serum.

It is generally agreed that in specific intestinal infections such as typhoid, paratyphoid and bacillary dysentery the causative organisms produce agglutinins in the patient's serum. Furthermore, *B. typhosus*, *B. paratyphosus* and *B. dysenteriae* are not found in the stools of normal cases except in occasional carriers who practically always give a history of having had typhoid or dysentery. *B. Morgan No. 1* does not fulfill either of these postulates so that it would seem improbable that this organism could be the specific cause of an intestinal infection like dysentery.

*B. pyocyanus*<sup>21</sup>, *Streptococcus fecalis*<sup>22, 23</sup> and *B. proteus*<sup>24, 25, 26</sup> can be similarly discounted as etiological agents in diarrhoea, for they are to be found in the stools of many normal children.

The theory<sup>27, 28</sup> advanced during the last century by French and German writers that infantile diarrhea was caused by highly virulent colon bacilli has died a natural death from lack of confirmation.

#### EPIDEMIOLOGY AND PREVENTION

Our studies in Birmingham revealed in many cases a well-defined history of contact infection from a neighbor's child or from an adult with a mild diarrhea; in several instances in Baltimore two cases occurred in the same house.

An examination of the source of the milk supply showed that the dairy could not be the origin of the infection. Studies in adult dysentery have shown that although wide-spread epidemics may occasionally be water-borne, dysentery bacilli are rarely recovered from central milk or water supplies.<sup>21, 22, 23</sup> It is sometimes maintained that inasmuch as the majority of the children suffering from dysentery are of the crawling age, the disease may be acquired through the child's fingers becoming soiled from the floor. It would appear in our series that the infection of the milk in the individual household by flies or the mother's fingers is also a possible explanation of its spread.

That the boiling of milk and milk mixtures before feeding has a most important influence on the prevention of diarrhoeal diseases has always been suspected and Knox and Powers<sup>24</sup> have found that the use of boiled milk mixtures in boiled containers has greatly reduced the incidence of dysentery among the children whose feedings have been supervised by the Babies Milk Fund Association of Baltimore.

That flies have been the means of carrying dysenteric infection has been clearly shown by the studies of Graham Smith<sup>25</sup> and others.<sup>26</sup> The epidemiology of the outbreaks of dysentery in Salonika<sup>27</sup> during the war has proven beyond a doubt that flies were offending agents during the summer months.

The curve (see Table IV) showing the data of onset of

TABLE IV.—INCIDENCE OF BALTIMORE DYSENTERY CASES

Month	1919 Cases	1920 Cases	1920 Cases	1920 Cases	1920 Cases										
Mar.	0														
Apr.															
May	0	2	4	1	8	4	3	3	2	3	0	0	0	0	0
June															
July															
Aug.															
Sept.															
Oct.															
Nov.															
Dec.															
Jan.															
Feb.															
Mar.															

our cases in Baltimore demonstrates that the majority of the cases occur during the height of the fly season. Table IV also shows the fallacy of calling dysentery in children "summer diarrhoea" for although the greatest incidence was in August, yet cases occurred regularly during the winter months.

Conradi in Metz<sup>28</sup> and Ohno in Japan<sup>29</sup> demonstrated *B. dysenteriae* in mild cases and normal individuals who had been in contact with dysentery patients during the winter months, so the probabilities are, that dysentery bacilli, which live with difficulty outside of the human body, weather the winter by means of chronic or mild cases or carriers and in the spring are ready for wider dissemination by flies.

The lesson to be drawn from these epidemiological studies is obvious. Children should be breast fed or given only boiled milk in boiled containers. Children and milk should be protected from flies. When cases occur, the stools should be completely covered so that flies do not have access. Almost invariably mothers will save specimens, for the visit of the doctor, either wrapped in a newspaper or in an imperfectly covered receptacle. Those engaged in caring for a patient with dysentery should not prepare food for other children. These recommendations seem self evident but they are necessary and are difficult to enforce rigidly.

Whether inoculations with dysentery vaccines will prove of value in children is problematical. Heretofore the severe reactions to these vaccines have prevented their use except in the face of a grave epidemic,<sup>30</sup> but the recent work of Graeme Gibson<sup>31</sup> in the British Army would seem to indicate that the reactions may be eliminated without impairing the value of the protection. Wholesale inoculations will probably never be necessary but eventually it may prove of value in cities that have a high incidence of infantile dysentery.

At present the treatment of this condition, as of typhoid fever, is merely palliative and does not seriously affect the mortality, yet the stamping out of this disease by suitable quarantine by Health Departments is an attractive possibility. This can only occur by recognizing that ileocolitis is caused by dysentery bacilli and reporting it as dysentery. Just as the clinical name of enteric fever was changed to typhoid and paratyphoid fever, so ileocolitis and infectious diarrhoea should be renamed in accordance with their etiology as dysentery in children. This plea was made in 1903 by Knox<sup>32</sup> following Duval and Bassett's pioneer work, but the old names still persist. One great advantage to be obtained from such a change of nomenclature would be the making of the disease reportable. In many of our cities dysentery is a reportable disease but ileocolitis attracts no official notice. Inasmuch as in our series of cases, bloody stools and a febrile onset are practically pathognomonic of dysentery, it would seem that the majority of cases can be recognized on clinical grounds and reported to the health authorities.

#### CONCLUSIONS

1. Over 80 per cent of the acute cases of ileocolitis both in Baltimore and Birmingham were due to infection with *B. dysenteriae*.

2. *B. dysenteriae* (Flexner) is more prevalent than *B. dysenteriae* (Shiga) in Baltimore, Maryland, and Birmingham, Alabama.

3. Clinically as well as bacteriologically the Baltimore and Birmingham cases were identical.

4. *B. dysenteriae* (either Flexner or Shiga) was not found in the stools of 63 cases of simple diarrhea nor in those of 100 normal children.

5. The name ileocolitis should be changed to dysentery in children and the disease made reportable to the health authorities.

6. Dysentery (ileocolitis) is probably spread from the stools of one patient to the food and mouths of other children by flies and infected hands and not disseminated from a general dairy source.

7. Dysentery is less prevalent among children receiving breast milk or boiled milk and boiled milk mixtures in boiled containers.

8. The agglutination reactions of the patient's serum by standardized technique is of assistance in the diagnosis of dysentery.

9. *B. Morgan No. 1*, *B. welchii*, *B. pyocyanus*, *B. proteus* and the *Streptococcus fecalis* are not the cause of dysentery (ileocolitis) or diarrhoea.

#### APPENDIX

##### BACTERIOLOGICAL AND SEROLOGICAL TECHNIQUE

**Stool Cultures.**—A loop full of bloody mucus (unwashed) was streaked first over the surface of one Endo plate,\* and then a second Endo plate without flaming the loop. After 18 hours' incubation at 37.5° C. the colorless colonies were fished into tubes of Russell's double sugar medium<sup>10</sup> (Andrade's<sup>11</sup> indicator). Those cultures that had colorless slants and red butts without gas after 18 hours' incubation were subcultured in gelatin and 7 Durham fermentation tubes of peptone water containing respectively 1 per cent of lactose, dextrose, mannite, maltose, saccharose, dulcite and rhamnose (Brom-cresol-purple indicator).<sup>12</sup>

The growth from the original culture (Russell's slant) was then emulsified in saline and agglutinated at 55° C. for four and one-half hours with polyvalent dysentery, Flexner and Shiga type, sera. Six- to eight-hour peptone water cultures were examined for motility and seven-day peptone water cultures were tested for indol by ether extraction and Ehrlich's reagent.<sup>†</sup>

\* Endo's medium employed was made as follows: Shred agar 20 grams; peptone (Difco) 10 grams; meat extract 5 grams; NaCl 5 grams; distilled or tap water 1000 c.c. Boil; adjust reaction to pH 7.8; filter and autoclave in 100 c.c. lots in flasks for 15 minutes at 15 lbs. Ten per cent lactose in distilled water was similarly autoclaved in 10 c.c. lots in test tubes.

To pour plates: Add 0.25 c.c. of 10 per cent basic fuchsin (in 95 per cent alcohol) to a flask of 100 c.c. of melted agar. Dissolve 0.5 gm. of sodium sulphite in a test tube of 10 c.c. of 10 per cent lactose and add the solution to the fuchsin agar. This will completely decolorize the agar. Pour into 7 100 mm. Petri dishes.

† Glynn's method.<sup>13</sup>

0.5 c.c. of ether was poured into the 7-day peptone water culture tube and the tube shaken. The supernatant ether was then pipetted off and stratified on 1.0 c.c. of distilled water in an agglutination tube. 0.25 c.c. of Ehrlich's reagent (paradimethylamidobenzaldehyde 4 parts; alcohol (95 per cent) 380 parts; hydrochloric acid (conc.) 80 parts) was then allowed to flow down the inside of the tube. A purple layer at the ether-water junction within 30 minutes denoted the presence of indol. This method obviates the difficulty of differentiating true indol reactions from the subsidiary colors due to the peptone culture media. Alternatively the Ehrlich reagent may be carefully added to the culture tube after shaking with ether so as to form a layer

The fermentation cultures were incubated at 37.5° C. and read at intervals, for over 21 days and the gelatin cultures were left at room temperature for 28 days.

The necessity for prolonged incubation of fermentation cultures is shown by the fact that 12 per cent of the cultures from children in this series and 29 per cent of those from the series in troops in the A. E. F. were late lactose fermenters, that is, colorless colonies on Endo's medium that fermented lactose after the second day of incubation. However, all fermentations were practically complete by the 14th day and only very slight changes occurred during the remaining time of the 21-day incubation. It would seem that 14 days' incubation for fermentation cultures is sufficient and not 21 days as often stated.

**Agglutination.**—Subsequent agglutination work to confirm the original tests was done with 18-hour peptone water cultures. For the diagnostic sera employed, I am indebted to the Rockefeller Institute for polyvalent dysentery, Flexner and Shiga, sera; to Dr. A. D. Gardner and the Medical Research Committee of England for typhoid, paratyphoid A and B, Shiga and Flexner V, W, X, Y and Z sera; to Captain E. G. D. Murray, R. A. M. C. for Kruse E, Schmitz, Shiga and Flexner V, W, X, Y and Z sera; and to Prof. F. W. Andrews for Z serum.

Dreyer's<sup>14, 15, 16</sup> technique was used to test the patient's serum for agglutinins. Inasmuch as I used eleven different antigens in this work I had to adopt the following modification of this method. The patient's serum (at least 1.0 c. c. was required) was diluted ten times. 0.5 c. c. (or 10 drops) of this diluted serum was placed in each of 11 agglutination tubes; 0.5 c. c. (or 10 drops) of a formalized standard agglutinative culture of each of the following organisms was placed in one of these 11 tubes; *B. typhosus*, *B. paratyphosus A*, *B. paratyphosus B*, *B. shigæ*, *B. dysenteriae* (Flexner), English types V, W, X, Y and Z, *B. dysenteriae* (Kruse E) (or *B. dispar*) and *B. dysenteriae* (Schmitz) (or *B. ambiguum*).

These tubes were incubated in a water bath at 55° C. for four and one-half hours. (Agglutination reactions with *B. dysenteriae* require longer incubation than those with *B. typhosus*. Four and one-half hours at 55° C. is the minimum time.) If agglutination was positive for any of these 11 cultures, tests were set up according to Dreyer's directions using only those standard agglutinative cultures for which there had been agglutinins in the preliminary test.

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## A STUDY OF THE BEHAVIOR OF SYPHILITIC AND NORMAL SERA TOWARDS CERTAIN COLLOIDAL SOLUTIONS

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The addition of a solution of protein, under favorable conditions, to many different colloidal solutions is followed after a certain time interval, often several hours, by a definite change in the mixture. Either a visible flocculus forms, or the solution "sets," or in some instances its color changes. The last outcome is best seen when solutions of colloidal gold are employed as in the Lange gold-sol reaction of the cerebrospinal fluid.

The reaction of protein solutions with various colloids was observed in connection with the Wassermann reaction early in the development of the test although its true significance was not then recognized.

Michaelis<sup>1</sup> added inactivated luetic serum to a properly diluted alcoholic extract of syphilitic liver antigen and incubated the mixture at 37° C. for five hours. At the end of that time definite flocculation was present in the tube containing luetic serum, and the controls (non-luetic serum) showed no turbidity. From this isolated observation he drew the false conclusion that the Wassermann reaction was a specific precipitin reaction.

Some time later Porges and Meier,<sup>2</sup> working with a lecithin colloidal solution, observed the same phenomenon. A one per cent alcoholic solution of lecithin was added drop by drop to physiological salt solution, with constant shaking, until the resulting mixture contained 0.2 per cent of lecithin. To one part of this colloidal solution an equal amount of inactivated human serum was added and the mixture was incubated at 37° C. for five hours. Various syphilitic and

non-syphilitic sera were tested in this way and the results controlled by complement fixation reactions. As a rule, flocculation occurred only in the tubes containing Wassermann positive sera, although the results were in many instances doubtful and in some cases false.

Recently Vernes<sup>3</sup> and his collaborators have studied the physical properties of luetic and non-luetic sera by the use of colloidal solutions of iron and of a cholesterinized organ extract colloid called by them "perethynol." The results of this work are of great interest and throw some new light on the complement fixation reaction in syphilis.

The important conclusions of Vernes may be briefly stated, although the original work must be consulted for details of the methods employed. These are:

1. Luetic sera differ from normal sera in their power to produce flocculation when added to colloidal solutions.

2. A few sera fall into a common zone where it is impossible to distinguish a syphilitic serum from a normal serum by flocculation reactions.

3. This zone varies with the colloidal solution employed and with the concentration of electrolytes.

4. The most accurate results were obtained by the use of sera which had been inactivated at 56° C. for 20 minutes.

These various observations show clearly that there is a physical difference between luetic and normal sera which can be demonstrated by very simple laboratory methods. Sachs and Georgi<sup>4</sup> have lately advocated the use of the flocculation reaction as a diagnostic test for syphilis, but the

reports<sup>5,6</sup> on its reliability have varied, no doubt owing to the technical difficulties encountered in determining the results. It seemed advisable, therefore, to study the phenomenon on sera controlled by the Wassermann reaction, using various colloidal solutions, electrolytes and H-ion concentrations.

#### METHODS AND REAGENTS

The following solutions were used in the preparation of colloidal solutions:

1. One per cent lecithin in alcohol.
2. Acetone insoluble antigen of Noguchi.
3. One per cent lecithin plus 0.2 per cent cholesterol in alcohol.

4. One per cent mastic in alcohol.
5. Various concentrations of sodium oleate in water.
6. Alcoholic beef heart extract plus 0.2 per cent cholesterol.

The colloidal solution was prepared by adding one of the above solutions drop by drop to physiological saline, with constant stirring, until the required concentration was obtained.

The sera were inactivated at 56° C. for 20 to 30 minutes, in a water-bath. Most sera were less than 24 hours old.

Various concentrations of NaCl,  $(\text{NH}_4)_2\text{SO}_4$  and  $\text{CaCl}_2$  were employed as electrolytes.

To carry out the reaction it is necessary to add to a series of clean, small test-tubes various amounts of colloidal solution, electrolyte and normal serum, and to a parallel series of tubes the same solutions in the same amounts, but replacing normal serum by known luetic serum. The tubes are then placed in an incubator at 37° for 15 to 20 hours, when the results are determined.

Flocculation is most easily seen by transmitted light, against a dark background, exactly as is the case when searching for a faint trace of albumin in the urine. The presence of heavy flocculation is easily determined as is the complete absence of a flocculus. If, however, there is a very fine but definite suspension of small refractile particles evenly suspended throughout the liquid, the result will depend on the size of the particles and the results of the controls. A barely visible flocculus is often present with known non-luetic sera and it is necessary to take account of this in reading the final result. A small hand-lens is of some help, but higher magnification will show that flocculation has occurred in practically every tube. Even with controls and the aid of magnification some results will be doubtful.

After numerous preliminary experiments to determine the influence of the various proportions of reagents and the effect of electrolytes, etc., the following conclusions were reached:

1. Inactivation of complement by heating the serum at 56° for 20 minutes is necessary to reduce the number of doubtful and falsely positive results.

2. A minimum amount of electrolyte is probably necessary, but this need not be over 1 per cent NaCl in the mixture. Eight per cent NaCl solution was used, but results were equally as good with 6 per cent and 10 per cent solutions.

3. H-ion concentration has no noticeable influence within the range of phenolsulphonephthalein as indicator.

4. Of the colloidal solutions used only an alcoholic extract of beef heart plus 0.2 per cent cholesterol, diluted 1:6 with physiological saline, was satisfactory.

The various reagents were employed in the following quantities:

Inactivated undiluted serum, 0.3 c. c.

Colloidal solution, 0.4 c. c.

Eight per cent NaCl solution, 0.6 c. c.

After these reagents were added, the tubes were shaken and incubated at 37° C. for 12 to 16 hours.

A known luetic and a non-luetic serum control were run with each series and each serum was controlled by replacing the colloidal solution by 0.4 c. c. of 15 per cent alcohol.

Two hundred sera were studied by this method and results compared with those of the Wassermann test on the same sera.

The following table shows the comparative results of the two reactions.

Results	Number	Wassermann reaction			Flocculation		
		Present	Absent	Doubtful	Present	Absent	Doubtful
*Positive .....	104	96	3	5			
Suggestive Positive .....	5	5	0	0			
Doubtful .....	19	14	1	4			
Suggestive Negative .....	13	5	3	5			
Negative .....	59	1	53	5			

\* The terms positive, suggestive positive, doubtful, suggestive negative and negative, mean respectively 75 per cent to 100 per cent fixation, 50 per cent fixation, more than 25 per cent fixation, less than 25 per cent fixation and slight or no fixation.

#### DISCUSSION

The results of the two reactions so closely parallel each other that it seems not improbable that complement fixation, as applied to the diagnosis of syphilis, may in some way depend on certain physical differences in the sera as shown by the increased floccability of luetic serum in the presence of certain colloidal solutions.

This belief is further strengthened by the numerous attempts to apply complement fixation as a diagnostic method in diseases of man other than syphilis. These have so far proved entirely satisfactory only in yaws, a disease closely resembling syphilis in certain other respects. It must be admitted, however, that the short-comings of complement fixation, as applied to the diagnosis of diseases other than lues, may possibly depend upon other factors than the one suggested—the properties of the serum. In this connection may be mentioned the difficulties encountered in securing suitable antigens, that is, ones that are not anticomplementary in dilutions which show good binding strength.

It seems desirable to study the subject of complement fixation in the light of certain colloidal reactions and to determine its relation to these reactions, for there is evidence to support the belief that complement fixation may occur only

in the presence of two colloidal solutions (serum + antigen, or serum + antiserum) which react by the formation of a flocculus.

#### CONCLUSIONS

1. Syphilitic sera can be shown to differ from normal in certain physical properties.
2. This physical difference is possibly of fundamental importance in complement fixation reactions, although at present its relation to immunity reactions is not clear.
3. The Wassermann reaction and the flocculation reaction closely parallel each other.

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## AN EXPERIMENTAL AND CLINICAL THERAPEUTIC STUDY OF WHOOPING-COUGH

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In a number of scientific communications published elsewhere, the author pointed out the interesting relationship existing between the chemical structure of the principal opium alkaloids and their pharmacological action on smooth muscle.<sup>1</sup> He has shown that these alkaloids can be sharply divided into two classes: the pyridin-phenanthrene group, of which morphin is the principal member, and the benzyl-isoquinolin group, of which papaverin is the principal representative. The morphin group is characterized by a stimulating action on smooth muscle structures, increasing their contractions and raising their tonus, while the papaverin group is characterized by a remarkable sedative effect on smooth muscle organs, tending to inhibit their contractions and to lower their tonus. It was further shown that the pharmacodynamic analysis of the papaverin effect pointed to the benzyl nucleus of the papaverin molecule as being responsible for the inhibitory and tonus-lowering action of papaverin and its related alkaloids. The reasons for these conclusions are to be found in detail in the author's papers. Following the above analysis of the papaverin action, the author described his search for and the successful discovery of a simpler compound containing the benzyl grouping and exhibiting the pharmacological properties of papaverin without its narcotic effects. It was shown that benzyl-benzoate actually produced all the pharmacological effects of papaverin on smooth muscle, but at the same time was much less toxic than that alkaloid on the other.<sup>2</sup> The therapeutic possibilities of benzyl-benzoate were then discussed and a series of clinical cases in which it had been used successfully were cited. The therapeutic indications for which the drug was recommended were those conditions of smooth muscle viscera which exhibited either an excessive peristalsis or excessive spasm, or both. Among such conditions were mentioned excessive peristalsis of the intestines, such as may be found in diarrhoea and dysentery, intestinal colic or entero-spasm, pyloro-spasm, uterine spasm,

spasmodic conditions of the gall-bladder and of the urinary bladder, ureteral colic, angio-spasm, and others. The author is happy to state that all these indications for the use of and therapeutic application of benzyl-benzoate, which were predicted on the basis of his work some three years ago,<sup>3</sup> have been fully sustained and corroborated through further experimental and extensive clinical data gathered since.<sup>4</sup> Furthermore, certain new and unexpected therapeutic uses for benzyl-benzoate have been discovered which were not known to the author when he first published his work on the subject, and one of these he proposes to describe in the present paper.

Among the most interesting spasmodic conditions of smooth muscle organs, for which the use of benzyl-benzoate was originally advocated, is bronchial spasm or true asthma. The author, at the present time, has on hand the records of some 200 such cases, 75 per cent of which have been successfully treated with the drug.<sup>5</sup> Furthermore, he has received similar reports from various outside sources including a communication from Dr. W. Storm van Leeuwen of Holland, describing a series of some 60 cases in which it has been tried with a very high percentage of successful results. The author noted long ago that even in cases in which the asthma was not completely relieved by benzyl-benzoate, a sedative effect on cough was produced by the drug and the bronchial secretions were rendered more fluid. Inasmuch as the general indications for the use of benzyl-benzoate in therapeutics have been described by the author as "spasmodic" conditions of the viscera, a number of physicians through a rather fallacious process of reasoning, inquired whether the drug might not be useful in spasmodic conditions of the larynx, such as are characteristic of whooping-cough. *A priori*, the author did not expect much benefit to result from its use in such conditions, inasmuch as the muscles involved in laryngeal spasms are not of the smooth, but of the striated variety. Nevertheless, inasmuch as the pathogenesis and pathological

physiology of pertussis is not quite clear, and inasmuch as, according to some authorities, the condition is also accompanied by more or less bronchial spasm; and furthermore, inasmuch as the author had already noted some slight sedative effect after benzyl-benzoate in cough, a trial of the drug in whooping-cough was deemed worth while and the author studied its effects in a number of patients suffering from that disease. The results were so unexpectedly gratifying that a more extensive study was soon undertaken. This could be conveniently done in Baltimore during the summer of 1918 because, at that time, an unusually severe and widespread epidemic of whooping-cough was present in that city. Through the co-operation of Dr. John D. Hogan, Assistant Commissioner of Health in charge of Communicable Diseases, the author was able to secure a large number of cases of whooping-cough which he carefully treated with benzyl-benzoate and other drugs directly under his own supervision. In this paper, it is proposed briefly to summarize the results of the clinical observations made and to report some experimental data obtained in the laboratory dealing with the mode of action of the drug in whooping-cough.

The number of cases studied was about 115. Of these a few were in adults; but the vast majority were in children ranging in ages from a few weeks to fourteen years. Many of these cases occurred in groups of two, three or more in one family; and owing to the prevalence of the epidemic and its severe form, the diagnosis of whooping-cough, in most cases, could very easily be made. All these cases were characterized by whooping and in many the paroxysms were accompanied by vomiting and small hemorrhages. In a number of cases, a blood examination was made and gave the characteristic blood picture of pertussis. Most of the patients before coming under the author's observation had been treated by parents or doctors with paregoric and other popular drugs without any benefit, while others had been left alone without any treatment whatever. A number of the patients received vaccine treatment, but the results in these cases were also not at all striking.

When a study of the cases was begun by the author, all other medication was discontinued and the patients were given a 20 per cent solution of benzyl-benzoate by mouth. The dosage varied from 5 to 40 drops in water, three or four times a day and oftener, depending upon the age of the patient and the severity of the disease. In cases in which the simple alcoholic solution of benzyl-benzoate was found to be too distasteful to the young patients, it was flavored with a few drops of benzaldehyde and the medicine was administered in sugar water or milk. The author soon noted that the addition of a little benzaldehyde to a solution of benzyl-benzoate in amounts varying from 1 per cent to 5 per cent produced a mixture which seemed to act more effectively in cases of whooping-cough than benzyl-benzoate alone. A possible explanation for this is given below. It was found that the administration of benzyl-benzoate in the form of a suspension in simple elixir, in syrup of yerba santa and

other syrups or elixirs was not a satisfactory method either of disguising the taste or administering the drug over long periods of time, as such mixtures are too bulky and unsightly and, in most cases, tend to disturb digestion even more than a benzyl-benzoate in alcohol would do in sensitive persons when administered without any flavoring.

The results of the clinical observations were as follows: About 90 per cent of all the patients showed more or less beneficial effects; about 50 per cent exhibited marked improvement in the symptoms. The therapeutic effects of benzyl-benzoate were not of a curative character but were of a distinctly palliative nature. These effects were manifested either by a reduction in the violence or in the number of paroxysms, or both; and also by the elimination of certain untoward sequelae following violent whooping, such as vomiting, sub-conjunctival hemorrhages, lack of sleep, and emaciation. In many cases, the relief afforded by the drug was so marked that the parents came begging for more of the drug and recommended it also to their friends. Many of the patients who responded favorably to benzyl-benzoate had been previously treated unsuccessfully with bromides, antipyrin, quinin, belladonna, paregoric, and even heroin. In some cases, the author purposely interchanged or alternated the benzyl treatment with one or other of the above drugs, and the difference in the therapeutic effects could be readily noticed. Among such cases were three of the author's own children who were suffering with whooping-cough in a severe form. These patients were given all kinds of whooping-cough remedies, including heroin. None proved to be in the least effective unless given in toxic doses (heroin). On the other hand, when the children were given a solution of benzyl-benzoate plus benzaldehyde, a most remarkable relief in the violence of the paroxysms as well as a decrease in their number, was noted. Whether benzyl-benzoate has any effect upon the duration of the disease, it is at present impossible to say. It is doubtful whether the drug will have any influence on the cause of the disease but there is no doubt whatever, from the author's experience, that in benzyl-benzoate we certainly have a valuable palliative preparation and the value of such a drug, in view of the disastrous consequences of repeated and violent whooping-paroxysms, needs no emphasis.

A very interesting question in connection with the effect of benzyl-benzoate on whooping-cough is: How does it act? To that end the author has been conducting a series of experiments during the past year and these experiments seem to indicate that the benzyl-effect in paroxysmal cough is exerted advantageously through a number of channels. The pathological physiology of whooping-cough is too complicated to be discussed in detail in the present paper; perhaps the best monograph on the subject is still that by G. Sticker in Nothnagel's *System*, to which the reader is referred. Briefly it may be stated that the two conditions which are conceded by all pathologists and clinicians to be present in whooping-cough are: (1) A catarrhal condition

of the larynx and other respiratory passages with a tenacious mucous secretion in the larynx; and (2) an excessive irritability or hypersensitiveness of the nervous mechanism of the larynx which readily induces a spasmodic contraction of the laryngeal muscles.

The pharmacological action of therapeutic doses of benzyl-benzoate in whooping-cough is apparently a manifold one. In the first place, the anti-spasmodic effect of the drug on bronchial spasm which very often accompanies the paroxysms, probably plays some rôle. Secondly, the author has conducted experiments in regard to the effect of benzyl-benzoate on the contractions of striated muscle and found that the drug is also a sedative for skeletal muscle though not, in the same degree, as in the case of smooth muscle.<sup>6</sup> In the third place—and this is probably of very great importance in the relief of the whooping paroxysms—the author found evidence that benzyl-benzoate probably exerts a slight anaesthetic effect on the larynx. It was found that the anaesthetic action so markedly exhibited by benzyl-alcohol, as described by the author elsewhere, is also exhibited in a high degree by benzaldehyde and to a lesser degree,<sup>7</sup> by benzyl-benzoate; and that both benzaldehyde and benzyl-benzoate when taken by mouth or even injected intravenously, are in part excreted in the saliva and the bronchial secretions. They therefore probably tend to diminish the sensitiveness of the otherwise excessively irritable mucosa of the larynx, and in that way prevent the vicious reflex which starts the paroxysms. Fourthly, the author has found through experimental studies on animals, as well as from clinical observations on patients, that the benzyl esters act as expectorants; and they therefore probably help to liquefy the tenacious clumps of mucus characteristic of whooping-cough, which are found in the larynx. Fifthly, the author has found from animal experiments and also from clinical observations that benzyl-benzoate is more or less of a sedative to the respiratory centre, and it would appear probable that this sedative effect upon the respiratory center is more marked in man than in the lower animals. Lastly, it is very possible that the antiseptic properties of benzaldehyde and benzyl esters<sup>8</sup> may play a rôle in combating the etiological factors of the disease.

It will be seen from the above considerations that the mode of action of benzyl-benzoate in whooping-cough is somewhat complicated. The effect of the drug in this condition is probably not a specific one, and indeed the author has used benzyl-benzoate with benzaldehyde successfully as a sedative in other forms of irritating spasmodic cough with viscid mucus.

As a result of a careful study of the cases treated by myself, I am inclined to believe that benzyl-benzoate, either alone or, still better, combined with a little benzaldehyde, is a valuable palliative or symptomatic remedy in pertussis. It is, of course, well known that in practical therapeutics, no measure will give a 100 per cent of successful results, so that a trial of the above treatment by other observers is very desirable. I should like especially to emphasize the very low toxicity of benzyl-benzoate, which would warrant its administration in even larger doses than those at first recommended. The dose of the drug to be employed will have to be determined by the physician in charge of each case. Thus, in a small series of about 30 cases of whooping-cough treated at my suggestion by officers of the Health Department of another city, the results obtained were much less promising than in my own cases, but later experience has convinced me that much better results would have been obtained had the dosage been somewhat larger than that recommended originally in this series of cases. On the other hand, reports from other sources seem to sustain my own original favorable experiences. More complete data of the experimental work in connection with this investigation and also further clinical experiences will appear in the *Journal of Pharmacology and Experimental Therapeutics*.

#### CONCLUSIONS

1. The administration of benzyl-benzoate solution alone and still better, in combination with small doses of benzaldehyde, exerts a beneficial palliative effect on the violence and number of whooping-cough paroxysms.
2. The mode of action of the drug in such cases has been investigated experimentally and is discussed in the text.
3. In view of the low toxicity of benzyl-benzoate and benzaldehyde, and the considerable number of successful therapeutic results obtained with them, their further trial in the symptomatic treatment of paroxysmal cough and especially of whooping-cough is deemed advisable.

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# THE PIGMENTED EPITHELIUM OF THE EMBRYO CHICK'S EYE STUDIED *IN VIVO* AND *IN VITRO*

## WITH SPECIAL REFERENCE TO THE ORIGIN AND DEVELOPMENT OF MELANIN PIGMENT

By DAVID T. SMITH

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### INTRODUCTION

The term *melanin* has been given to a varied and complex group of pigments which give the color to the hair, eyes, and skin in man, and are also responsible for the color of most of the birds, animals, and insects (Gortner, 1911). According to Gortner, the melanins may be divided into at least two classes: (1) The melano-proteins, which are soluble in dilute acid but not in ordinary organic solvents; when hydrolyzed with strong acids these yield tyrosin, lysin, arginin, and an unidentified brownish black residue. Pigment of this type is found in auburn hair, appearing as a diffuse color and not in the form of granules. (2) The melanin proper, which is the more abundant type, occurs generally in the form of small granules. It is not soluble in dilute acid or in any of the usual solvents.

It is generally believed that pigment is produced by the action of an oxidase on an oxidizable chromogen (Gortner, 1911). This oxidase is called *tyrosinase*, because of the fact that it acts on tyrosin and other aromatic compounds containing a hydroxyl group (Bertrand, 1896, 1908). Its reaction is supposed to produce a melanin-like pigment; indeed, von Furth and Schneider (1901) were able to isolate a tyrosinase from the hemolymph of Lepidopteran larvæ which, when treated with tyrosin, produced a black pigment. This artificial melanin had all the chemical properties of natural melanin; on analysis it gave practically the same proportions of carbon, nitrogen, and hydrogen as had been obtained from the melanin pigment of the negro skin (Abel and Davis, 1896). Gessard (1903) found tyrosinase in the ink-sac of the cuttlefish and in melanotic tumors of the horse. In fact, it has been found by various investigators to be widely distributed in tissues where it may give rise to melanin by an oxidation of the chromogen (Kastle, 1909).

The nature of the oxidizable chromogen has received quite as much attention as the oxidizing agent. Von Nathusius (1894) found that when white hair was subjected to boiling in aqueous solution of methyl-green, minute, deeply colored particles could be seen which corresponded in size and position to the pigment granules in black hair. He therefore concluded that the same histological element is present in both white and black hair, except that in the former it is colorless. Abel and Davis (1896) found that the pigment granules of the negro's skin and hair could be partially decolorized by heating with ammonia and alcohol and that they would then stain strongly with gentian violet.

In 1889 Mertsching proposed the theory that melanin was formed by the breaking down of the cell, especially of the nucleus. Rosse (1904), studying pigment formation in melano-sarcoma, came to the conclusion that pigment was produced by the extrusion of small particles of nuclear material and that the nucleus was impoverished thereby. Schultz (1912) studied a case of mycosis fungoides and he, too, decided that the oxidizable chromogen is derived from the nucleus. Aurel von Szily (1911) observed the formation of melanin pigment in the developing eye of a variety of vertebrates, including the hen, and also described pigment formation in melanotic tumors of the human eye. He concluded that the pigment came out of the nucleus as colorless, rod-shaped granules, which later became colored as they wandered about in the cytoplasm of the cell, probably by the action of cell ferment. This coloring did not take place simultaneously in all parts of the granule, but began at one end and proceeded to the other. The production of pigment took place with or without degeneration in the nucleus.

Dyson (1911) held the theory that the pigment is developed from a lipochrome which he believed to be a product of the nucleus. Certain other observers have been unable to find any evidence that the granules come from the nucleus and believe that they develop from the mitochondria. Champy (1911) denied their nuclear origin and described thread-like mitochondria breaking into fusiform granules that were at first colorless but later became colored. He was the first observer to note that the granules appeared to collect about the centriole (Nebenkern). Leplat (1912) did not observe any definite arrangement about the centriole, but he, too, believed that the pigment was probably derived from the mitochondria. The same conclusion was reached by Luna (1913) who studied melanin pigment in the eye of embryo frogs and chicks.

Strong (1902) advanced the theory that the pigment granules arise within the cytoplasm of the cell and gave a detailed study of the fundaments of the feather showing this to be the case. He stated that "the pigment arises in the form of grayish or light yellow corpuscles of exceedingly small size, arranged along delicate protoplasmic strands which radiate from the nucleus." He does not mention the centrosphere but some of the drawings, as well as the photographs, given in his paper show the pigment granules arranged at one side of the nucleus around what is undoubtedly the centrosphere.

Hooker (1915) began his investigations of the subject with the tissue culture method. He studied the melanophoric cells of the frog larvae cultivated in plasma and observed the formation of pigment, but found no evidence that it was derived from nuclear substance, nor did he see any signs of the colorless granules described by von Szily. He concluded that the pigment was formed from material in solution in the cytoplasm, and that the nucleus was active in the production of an oxidase which acted on this soluble chromogen. In 1917 Luna cultivated the pigment epithelium of the eye of embryo chicks in plasma, but was not able to find any evidence that the mitochondria changed to pigment in the cultures. He still contended, however, that such a change might take place in the living embryo.

It will be seen from this brief review that the theories concerning the origin of the pigment granules are decidedly at variance, different authors claiming respectively that their source is (1) the nucleus, (2) the mitochondria, and (3) the cytoplasm.

I wish to acknowledge the valuable assistance and encouragement of Mrs. Lewis and Prof. W. H. Lewis, in whose laboratory these observations were made.

#### TECHNIQUE

The pigment layer of the retina of the chick embryo (5 to 15 days' incubation) was chosen for study. The tissue was removed and pieces of it explanted in Locke-Lewis solution according to the method employed by Lewis and Lewis (1915). Other explants were made in plasma by the Burrows (1910) method. Film preparations were also made by placing a piece of the pigmented layer in a drop of Locke-Lewis solution and covering it with a coverglass. If just the right amount of fluid is extracted from under the coverslip the pressure caused by the weight of the coverslip spreads the cells out thin and thus they can be observed with advantage under the microscope. Fixed and stained preparations, made from both the cultures and the films, were studied for a comparison with the methods of other observers. The living cultures were stained with neutral red and Janus green. One series of cultures were grown in Locke-Lewis solution containing neutral red; after the pigment granules had taken up the red stain, a number of these cultures were fixed in Zenker's fluid from which the acetic acid had been omitted and stained with iron hematoxylin. Zenker's without acetic acid was used most frequently as the fixing agent. Various preparations were stained with iron hematoxylin, crystal violet, safranin, anilin fuchsin, aurantia, toluidin blue, and eosin.

These methods were followed in order to observe directly, if possible, whether the mitochondria change into pigment granules or whether the granules arise independently in the cytoplasm, and also to see what changes in color, size, and shape take place in the granules during their development. Furthermore, if the granules were extruded from the nucleus, as described by some investigators, I concluded that it should be possible to observe the process under the microscope.

#### OBSERVATIONS

In order to get an adequate idea of how the pigment cells of the living retina appear unstained, film preparations were made. The eye of an eight-day chick embryo was removed and dissected, the pigment layer being stripped off carefully from the underlying choroid. Films were then made from the pigment layer and studied with an oil-immersion lens. A membrane of rather large hexagonal cells was found; the nuclei could be made out distinctly, but the remainder of the cytoplasm was densely packed with dark brown or black rod-like granules. On this account no mitochondria could be seen.

Another egg was opened, the pigment layer of the retina peeled out, and tiny pieces were explanted by the Lewis method. In five or six hours connective-tissue cells from the choroid began to grow out. In one case retinal cells also appeared, but usually the pigment cells were not observed before fifteen to thirty hours.

Along the free edge of the cell clear protoplasm was seen to flow out (Figs. 1 and 2), forming a transparent border in sharp contrast to the black pigmented body of the cell. This protoplasm at first contained neither pigment granules nor mitochondria. The advancing protoplasm put out processes along the under surface of the coverglass after the manner of amoebæ, although much more slowly. When an obstacle was encountered or the temperature became unfavorable, these processes were rather rapidly withdrawn; however, in their retreat they left enough of their substance on the coverglass, in the form of a slight smear, to reveal where they had been. After the processes had moved out a convenient distance, they seemed to anchor themselves to the glass and to draw outward bodily the remainder of the cell. This procedure was repeated until the proximal part of the cell was pulled out from the original mass. The migration was relatively slow and generally took several hours for its completion. The migrating cells were not separated entirely from the original mass; each one was connected with the cell immediately behind and with the one on either side, so that when the first moved out it drew the other three after it. These cells in turn repeated the process until a membrane of cells was formed (Fig. 1).

In one culture the cells did not grow out in the membrane formation just described, but were joined to one another by their ends like connective-tissue cells. Luna (1917) described and figured both types of growth. The cells that were farthest from the original piece were very thin and spread out over an area two to two and a half times as large as that occupied by the original cell. Those nearer the explant approached nearer the dimensions of the original cells. The thin cells on the periphery were used for study.

There was little difference observed between refraction of the nucleus and that of the cytoplasm. Most of the granules were concentrated into a large mass at one side or one end of the nucleus (Fig. 2), probably about the centriole or centrosphere, in much the same manner as the degenerating granules

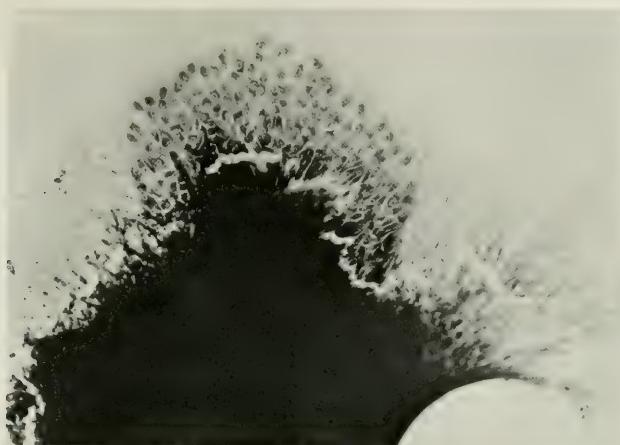


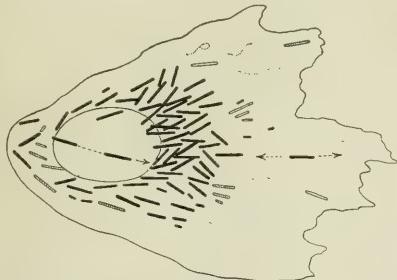
FIG. 1.—Photograph of a 72-hour growth from the pigment layer of the eye of an 8-day chick embryo in Locke-Lewis solution. The darker membrane is the growth of pigment cells. The spindle-shaped cells on each side are fibroblasts. The growth broke away from the explant when mounted.



FIG. 2.—A photograph taken with a higher magnification ( $\times 550$ ) of the left area of the pigment epithelium shown in Fig. 1. In most of the cells the pigment granules are massed around the centrosphere at one side of the nucleus.



and vacuoles observed in fibroblasts by W. H. Lewis (1919). From this mass granules extended out in all directions and in some cells surrounded the nucleus. Schmidt (1917) also observed this phenomenon. The nucleus and the mass of granules occupied the proximal three-fifths of the cell. The distal two-fifths was composed of relatively clear cytoplasm in which mitochondria and scattered pigment granules could be seen (text fig.). The mitochondria were generally in the form of filaments or rods and were seen to move slowly about in the cytoplasm. The pigment granules were usually plump rods, the length varying from one and a half to five times their width. Nearly all the cultures contained a few perfectly round ones also, the number being greater in some cultures than in others. The larger granules were estimated to be from two to three times as large as those found in the human skin. In color they were for the most part between dark brown and black, although various shades of gray could also be seen. The great majority of the granules were of maximum size and black in color. Regardless of the shade, however, the color of each individual granule was homogeneous.



TEXT FIG.—A diagrammatic representation of a cell from the growth of pigment epithelium, showing the various types of pigment granules found at different stages in the development of the pigment. The thin threads are the mitochondria. The stippled granules represent the gray pigment granules while the clear and the black bodies are intended to show the different sizes and shapes of the colorless and black pigment granules.

When the culture is first placed under the microscope the pigment granules show little signs of activity, but under the influence of light and heat their movement is accelerated. They move in the cytoplasm with a swift, jerky motion, starting off with a jump, going a little way, stopping suddenly for a second or two, and then starting off with another spurt. Some of them show a tendency to move in definite paths back and forth from a point near the nucleus to the periphery. Sometimes this journey is made with only the one stop at the periphery; at others it is accomplished by a series of spurts. When the granule reaches the periphery it may or may not reverse ends before coming back. It is estimated that at the minimum it required about 3 seconds to reach the periphery, 2 seconds to reverse or rest, and 3 seconds to return. Some granules move about in the cytoplasm in an apparently aimless manner. When in motion the granules may strike the mitochondria, bend them aside, and go in; in fact, a pig-

ment granule may plough through a relatively thick mass of mitochondria.

The granules were found to migrate much farther out into the peripheral processes than do the mitochondria. They have also been observed to move entirely across the nucleus. Those which in Fig. 2 appear to be in the nucleus were actually in the cytoplasm between the nuclear and the cytoplasmic membranes.

In all of the cultures some granules were observed to be free in the culture fluid. This was due to the destruction of a certain number of pigment-bearing cells in the process of explanting the tissue. In cultures planted in Locke-Lewis solution these free granules underwent Brownian motion. Each culture contained also a certain number of blood cells carried over with the explant from the ruptured vessels of the choroid. The red blood cells, all of which were of course nucleated, showed no tendency to take up the loose granules. The clastomocytes, on the contrary, did so readily and sometimes appeared quite black with granules. Some of the connective-tissue cells also took up the pigment granules, but this phagocytosis was more limited in extent than that in the clastomocytes, rarely more than three or four granules being ingested by a single cell. They appeared usually to be taken directly into the cytoplasm and not into vacuoles. Some were seen to move in the cytoplasm of these connective-tissue cells, but their motion was not characteristic nor was it anything like so extensive as in the epithelial cells.

A peculiar change took place in some of the granules that had been taken up by the connective-tissue cells; they appeared to swell up and there was a relative if not an actual decrease in color. Whether the process would have gone on until there was a complete decolorization of the granule was not determined. Such decolorization did not take place in the granules of the pigment epithelium grown in Locke-Lewis solution, even when incubated as long as a month.

When neutral red was applied to a culture it was found that the pigment granules took the stain. The longer the stain was allowed to act, the deeper was the color. When a little neutral red was added to the culture medium and the cells were grown in it, the granules became decidedly red. Furthermore, even after such a culture was fixed in Zenker's fluid (without acetic acid), cleared, stained with iron hæmatoxylin, and mounted in balsam, the granules still retained the red color. In some specimens it was still marked at the end of nine months. The gray granules seemed to take the red even better than the black ones. When a combination of neutral red and janus green was applied to a culture it brought out the mitochondria and the pigment granules in sharp distinction. The mitochondria stained bright blue with the janus, while the pigment granules took up the red. Lewis and Lewis (1915), W. H. Lewis (1919), and others have shown that the neutral red does not stain the mitochondria. They have also shown that the "neutral red bodies," which take the red in the living cell, lose their color on the death of the cell. Hence, so far as we know, only the pigment gran-

ules are capable of keeping the neutral red stain after fixation and mounting. This staining reaction offers, therefore, a simple method by which the pigment granules can be differentiated from other cellular elements. The peculiar pigment granules described above in certain of the connective-tissue cells failed to stain with janus green but stained quite readily with neutral red.

The age at which degeneration begins in cultures grown in Locke-Lewis solution cannot be given accurately, as it may range from 24 hours to 5 days. It can be brought about at any age by allowing the temperature of the warm box to rise from 39° to 45° C. The first sign of degeneration is the formation of tiny vacuoles in the cytoplasm, accompanied by changes in the mitochondria, some of the filaments breaking up into short rods and forming tiny vesicles. The vacuoles increase rapidly in number and in size. A few fat droplets also appear in the cytoplasm. After the vacuoles have reached a fair size, blebs are seen to form in the wall of the cytoplasmic membrane. From this stage on the nucleus becomes more and more refractive. The blebs contain a fluid that has a different index of refraction from the cytoplasm. At first they change in size and shape with a fair degree of rapidity, but later become more stable. Pigment granules are often drawn into these blebs, and when this occurs the granules lose their characteristic movement and exhibit Brownian motion. The process continues until the cytoplasm is a mass of vacuoles; the nucleus then begins to break up, the cell loses its definite outline and the vacuoles themselves break up. Strange to say, however, the pigment granules are not destroyed by these reactions. I found them holding their size, shape, color, and relative positions, although spread out over a larger area. It is possible to estimate from them the size and shape of the obliterated cell, very much as one would estimate the size and shape of a man from his skeleton. The time required for the completion of the degenerative process may range from 24 hours to a week or more.

Control cultures made in plasma gave practically the same picture of growth and degeneration.

Luna (1917) studied the pigment cells exclusively in plasma cultures, and gave an excellent description of their normal growth, which is essentially the same as the above. He claimed that no mitotic division took place but described what appears to have been direct division in a few cells that became detached from the growth and were in the process of degeneration. Uhlenhuth (1914) found no division of any kind in the pigment epithelium of the frog's retina. In the author's investigations, likewise, no division of the cells was observed.

A more detailed consideration of the various intracellular structures, *i. e.*, mitochondria, pigment granules, neutral red bodies, and fat droplets, together with their relation to each other, is given below.

#### MITOCHONDRIA

The mitochondria could be carefully studied in the thin peripheral cells. They occurred mainly as filaments and rods

and appeared to be slowly wafted about in the cytoplasm of the cell by intracellular currents (?). The filaments were seen to bend on themselves, forming triangles, circles, loops, and corkscrew forms, but these later straightened out again or changed to some other figures. Although cultures were observed continuously for hours at a time, absolutely no indication of the mitochondria being changed into pigment granules was seen. Luna reported similar results from his observations. The mitochondria were stained in the living cell with janus green. Cowdry (1914) and Lewis and Lewis (1915) as well as others, have shown that janus green colors the mitochondria and differentiates them from the cytoplasm and from the other cellular elements. In my observations the janus green stained the mitochondria a bright blue, but uniformly failed to stain any granule that had a particle of brown or black in it.

As noted above, Luna (1917) assumed that the mitochondria might turn into pigment granules in the eye of the living embryo, although he failed to observe that they did so in his cultures. To test this point the author made fresh spreads of the pigment layer taken from the eye of living embryos of 3 to 5 days' incubation and stained them with janus green. These ages were chosen because it had been previously determined that pigment production was most active at this time. None of the granules that had any color, or even the characteristic rod shape, took up the stain.

#### MELANIN PIGMENT GRANULES

The general appearance and behavior of pigment granules in cultures have been described above. In view of the various theories as to the origin of these granules, it was deemed of interest to determine at what hour of incubation and in what form they first appear in the cell. Accordingly, series of preparations of embryos ranging from 5 days down to 42 hours of incubation were made with the aid of a dissecting microscope. In embryos of 3 to 5 days' incubation the optic vesicle was opened and the pigmented epithelial layer of the retina teased out. Small pieces were studied fresh and also after fixation in Zenker's fluid without acetic acid. The fresh material was stained with janus green and neutral red and studied in a warm box. In the fixed material small pieces of the pigmented tissue were transferred in a pipette to a coverglass and the excess fluid was removed with a pipette. A drop of Zenker's fluid, without acetic acid, was placed on a slide, and carefully covered with the coverslip, the cells being flattened out by gentle pressure on the coverslip. The preparation was then sealed with vaseline to prevent evaporation. The fixing solution was allowed to act from two to four hours. The length of time necessary for good fixation was determined by the appearance of the tissue under the microscope. After fixation the vaseline was removed and the coverslip separated from the slide, the tissue usually adhering to it. The preparation was then cleared by the usual method. This treatment gave good results because the pigmented membrane was composed of a single layer of cells. For prepara-

tions between 3 days and 42 hours the whole eye was teased out into tiny pieces after it had been transferred to the cover-glass. It was then fixed in Zenker's and carried through the procedure described above. One such series was mounted unstained in order to get the variations in the color of the granules at the different ages. Other series were stained with various dyes as will be described farther on.

At 42 hours the optic cup is not yet invaginated. The pigment-bearing cells, by reason of their large-sized, characteristic, large, round nucleus, and a relatively small amount of cytoplasm, could be readily distinguished from the cells that were to form the visual elements. A few of these pigment cells exhibited signs of granules. An occasional gray or colorless granule of small or medium size was seen, but none were found that were black when exposed to the full light of the microscope; neither were there any that could be called full grown. Neutral red was applied as a vital dye to one such preparation and after staining had taken place the tissue was fixed in Zenker's. The granules that contained some black and those that appeared colorless both took the red. In addition, small red granules could be seen that were invisible before. This would indicate that these granules were of the same material as the larger ones.

In a 48-hour embryo the circulation is very active. An unstained specimen of this stage showed an increase in the number of grayish black granules, although none of them were as yet of maximum size and color. Staining with neutral red showed that there was a considerable increase in the number of the small red granules.

In the eye of a 60-hour embryo some of the medium-sized granules and some very small ones were found to be black even when exposed to the full light of the microscope. As in the younger embryos, various shades of gray were seen. The neutral red brought into evidence a large number of the small red ones, many of which were in the form of plump rods.

At the 66-hour stage the retina contained a few granules of maximum size and color. Wide variations in color were noted; some of the smallest granules were dark while some of the medium-sized ones were almost colorless. Neutral red gave the same picture as that mentioned above.

An unstained preparation from the eye of a 72-hour embryo showed a considerable increase in the number of black granules of all sizes. One of the fixed specimens was stained with an alcoholic solution of crystal violet. The entire cell took the stain diffusely but the granules were stained more deeply and stood out quite well, even the very small ones being visible. Some of these were even a little smaller than those demonstrated with the neutral red. Toluidin blue also stained the granules but not so well as the crystal violet.

The 78-hour specimen showed the same picture but more advanced. Each cell contained from 10 to 25 granules, including a number of small black ones. Aurantia, toluidin blue, and crystal violet all stained the granules.

In preparations of a 96-hour embryo the granules appeared to have about doubled in number in the preceding 18 hours.

The variations in size and color were practically the same as recorded above.

At 120 hours the granules had increased to such an extent that it was impossible to count them. There was a much larger proportion of medium and larger sized ones than were found in younger stages. There remained, however, more of the small and the gray granules than are present in the fully developed eye.

In not one of the series was there any indication that the granules were extruded from the nucleus. The nuclear membrane appeared always intact. The granules, so far as it was possible to tell by simple observation, were always in the cytoplasm and never in the nucleus.

It was thought that signs of pigment production were detected in cultures made from embryos of 5 to 15 days, but this could not be determined accurately because of the large number and active movement of the granules. Accordingly, cultures were made from the eye of 2-day chick embryos, at which stage the granules are small and few in number and are not of maximum blackness. Because of the very small size of the eyes at this time only one explant could be made from each. Hen plasma, Locke-Lewis solution, and a mixture of the two were used respectively as culture media.

The cells did not exhibit amoeboid motion and did not grow out, but along the edge of the tissue individual cells were found that were thin enough to allow accurate observation. After 4 days' incubation there was a slight but definite increase in the number, size, and depth of color of the granules. Nevertheless, we must conclude from these, as from previous experiments that pigment production is not active in tissue cultures.

It may be noted that in some of the preparations crystal violet was used to stain the pigment granules. It is well known that crystal violet is used in the Benda method as a mitochondrial stain. This does not indicate, however, that the granules are of mitochondrial substance, as will be seen by the following experiments.

A few pigment-bearing cells were spread out on a slide. The cells were broken up to a great extent, leaving many of the granules free on the slide like bacteria. The preparation was then stained with an alcoholic solution of crystal violet. The granules, which in the fresh material appeared as dark brown or black, were now tan in color. On the other hand, the granules that had appeared gray or colorless in the fresh were violet in color. These varied in size from the usual pigment granule down to the limits of visibility. Several of these smears were made and all gave the same result. One of them was treated with cold concentrated HCl for two hours. The color of the stain was removed by the acid, but when the smear was restained the pigment granules, from the largest down to the smallest, were found to be intact. The cell outlines had partially disappeared and what remained had changed to a homogeneous, blue-staining mass. Some of the granules that before had looked dark tan, now appeared purplish. The acid experiment was repeated several times

with intact cells that had been previously fixed in Zenker's. Sometimes the cell outlines were not entirely destroyed, but the nucleus and the cytoplasm were reduced to a bluish-staining mass in which could be seen the intact pigment granules of various sizes. In cells from the choroid, used for control, these small, purple-staining granules could not be found. Since neither the large nor the small pigment granules were affected by the HCl, whereas mitochondria are destroyed by weak acetic acid, we must conclude that these two cellular elements are probably different chemically.

The exact chemical structure of the pigment has not been determined. Hirschfeld (1889) found the pigment granules in the eye of the ox to be composed of a protein stroma and a dark brown amorphous pigment. His analysis of the pigment showed neither iron nor sulphur. From this he concluded that it was not a derivative of hemoglobin. His conclusion as to the absence of iron has been supported by Abel and Davis (1896) and a host of other chemists. Abel and Davis found that the pigment granules of the negro's skin and hair could be separated into a colorless protein stroma and a dark brown amorphous powder by treating with HCl, followed by boiling in weak alkali for a considerable length of time. The pigment was found to contain sulphur but no iron.

Repeating the work of several investigators, I decolorized these granules with hydrogen peroxide and potassium permanganate. After this process the granules still retained their size, shape, and general appearance except for the loss of color; they could then be stained with any of the stains mentioned above.

#### NEUTRAL RED BODIES

The neutral red granules that have been described in tissue cultures by W. H. Lewis, are few in number or entirely absent in normal young growths of retinal cells. They appear and increase in number with the age of the culture but are never seen in the pigment cells to the same extent as in connective-tissue cells growing in the same culture. There is little danger of confusing the small, colorless pigment granules with the neutral red bodies for the following reasons: (1) The colorless pigment granule is present in the cell before the neutral red granule makes its appearance. (2) The tiny pigment granules usually have a uniform rod shape with an index of refraction that is slightly different from that of the neutral red body. (3) The pigment granule, when stained, holds its red color even after fixation and mounting, while the other type of granule disappears at the death of the cell.

#### FAT DROPLETS

The amount of fat found in these cells varies with the condition of the culture and with the nature of the medium. Cultures grown in Locke-Lewis solution contain very little fat. Practically no visible fat is found in young cells grown in this medium, but as the cells degenerate some fine globules make their appearance. These can be stained with Sudan III. If the cultures are grown in plasma from a fat hen, even the

young cells are found to contain quite a number of large fat droplets which have evidently been absorbed from the plasma (Lambert, 1913). A study of the living pigmented epithelial cell did not show any connection between the pigment granules and the fat globules. So far as could be seen, the fat globules present in the cell took no part in the formation of the pigment granules, neither were the pigment granules in any way related to the formation of the fat globules.

#### DISCUSSION

In the introduction it was noted that some workers hold the theory that the pigment granules arise from the nucleus, others, that they are derived from the mitochondria, while Hooker believes that they originate in the cytoplasm. Aurel von Szily (1911) is one of the foremost of those who consider the nucleus responsible for the granules. His results are the more readily compared with my own because a part of his work was done on the embryo chick's eye. He stated that pigment production may take place with or without degeneration of the nucleus. He described the nucleus as extruding a colorless granule which became colored as it wandered about in the cell, the coloration beginning at one end of the granule and proceeding to the other. He gives numerous figures to illustrate this process.

Certainly in my own series I found no signs of nuclear degeneration. That there are colorless granules in these cells during the stage of active pigment production is confirmed by the observations herein recorded, but the results do not lend support to von Szily's theory as to the process of coloration. With the idea of determining this point hundreds of granules of various shades were examined carefully, and in every instance the granule was found to be homogeneous in color. In justification of von Szily, it may be said that at first sight many of the granules appeared to be black at one end and light at the other. Sometimes this was found to be due to the fact that they were viewed from an angle, in which case the end which was in focus was black while the end that was slightly out of focus appeared gray. By careful focusing, the black could be made to move from one end of the granule to the other, showing that it was really black in color throughout. At other times the appearance of one black end was due to an overlying or crossing of the granules at various angles. No granules were ever observed in the nucleus, although often they were seen to move over the surface of the nucleus and on out into the cytoplasm. In fixed preparations many of these granules undoubtedly appear to be coming out of the nucleus. It is possible that this is what von Szily has described. His final point in favor of a nuclear origin is the fact that the granules stain with a nuclear stain. This is true; but they likewise stain with cytoplasmic stains. Schultz (1912), who supports the nuclear theory, describes small pigment granules in the cytoplasm some of which stain with eosin and others with basic dyes. I am inclined to believe that the proof offered for a nuclear origin of the pigment granules is not conclusive, at any rate in the chick.

Those who support the mitochondrial theory base their conclusions largely on the following observations: (1) There is a similarity in appearance between certain of the mitochondrial forms and the small gray or colorless pigment granules. (2) They give a similar staining reaction with certain stains. (3) The mitochondria are supposed to disappear as the pigment granules appear in the cell.

1. It is fair to assume that if there is any change from mitochondria to pigment granules such transition would be from the mitochondria to the least differentiated form of the pigment series, which happens to be the small, colorless granule. My own investigations afford the following evidence against such a theory: (a) These colorless pigment granules are not so refractive to light as the mitochondria; (b) in an extensive study of the mitochondria in the living cell no change to pigment granules was detected (Luna, 1917, records a similar result); (c) films made from the eyes of embryos during the stages of most active pigment production and stained with janus green and neutral red, gave no indication that the mitochondria were being changed into pigment; (d) these small granules have the shape and the characteristic jerky movement of the larger pigment granules and nothing of the slow drifting motion of the mitochondria; (e) the colorless granules are much more stable than the mitochondria—they are not destroyed by acetic acid nor even by concentrated HCl.

2. In regard to the reported results that the colorless granules stain like mitochondria, my observations yielded contradictory evidence. While it may be true that after fixation these granules stain with certain dyes just as do the mitochondria, it does not necessarily follow that they are the same structure. Duesberg (1910) states that, although certain structures in the spermatid of *Blatta Germanica* stain like the mitochondria, they are in all probability not mitochondria. This heterogeneous staining is well known in connection with many of the usual histological methods. Fortunately, we are not dependent upon fixed tissue stains alone for the determination of this point. In the living cell these colorless granules are not stained by janus green, which is recognized as a specific mitochondrial stain (Cowdry, 1914; Lewis and Lewis, 1915). They stain readily with neutral red which Lewis (1919) has shown does not stain the mitochondria in the fibroblasts of tissue cultures. Their physical appearance and behavior, their resistance to strong acid, and their staining reactions identify the colorless granules with the stroma of the larger granules which is known to be very different chemically from the mitochondria.

3. If the mitochondria do actually disappear as the pigment increases in the cell it can be readily seen that this would be an important point in favor of the mitochondrial theory. As shown by his figures, Luna (1917) found numerous mitochondria in cultures of retinae of the same ages as those from which he had previously (1913) drawn the conclusion from a study of fixed material that the mitochondria had disappeared with the advent of pigment formation. In our cultures the cells of the pigmented membrane contained about

the same amount of mitochondria, regardless of the embryonic stage or the amount of pigment present in the cell. The natural conclusion from this is that the mitochondria do not decrease with the increase of pigment.

Hooker's conclusion that the granules arise in the cytoplasm of the cell comes nearer to fitting the known facts, although he did not find colorless granules in the epithelial cells of the frog. He holds the view that an oxidase acts on a soluble chromogen and produces a black pigment. This may be correct for the frog, but in the chick's eye it is evident that the process may take place in two distinct stages: (1) The formation of a colorless chromogen, which is shown by the presence of colorless granules in the younger stages of development; (2) the production of color in this chromogen, probably by the action of cell ferment. This is shown by the various shades of gray found among these granules and by the fact that the gray ones have practically disappeared from the fully developed eye. In general it may be said that these two processes go on at the same time. Hence we get a small black granule in the cytoplasm which grows by accretion (?) into a large black granule. That the granules actually grow in the cytoplasm of the cell is shown by the fact there is a gradual change from a large number of small granules and relatively few large ones in the younger ages to a large number of "full grown" granules and only a few small ones in the fully developed eye. This gradual increase in the size of the granules with the age of the embryo is recorded by Luna (1913, 1917). Furthermore, granules have been seen to increase in size in cultures made from the eyes of 2-day chick embryos.

#### CONCLUSIONS

1. Tissue culture affords an excellent method for the study of the pigmented cells in the retina of the chick. The pigment cells migrate out on the under surface of the cover-glass and spread out in the form of a thin membrane, thus offering an excellent opportunity to observe the behavior of the different granules found in their cytoplasm.

2. No cell division of any kind was observed in these cultures from the pigmented layer of the retina.

3. The production of pigment in tissue cultures is limited in extent.

4. The pigment granules are very stable. Even the small colorless and small gray ones are not destroyed by cold concentrated HCl.

5. The pigment granules move in the cytoplasm of the cell with a swift, jerky motion, which is much accelerated by continuous exposure to light.

6. They tend to concentrate about the centriole or centrosphere and to move in radiating paths between the centriole and the periphery, or vice versa.

7. When the cells are grown in a medium that contains neutral red, or when exposed to its action for a considerable length of time, the pigment granules stain with neutral red and retain it even after fixation. Other granules in these cells may take up neutral red but these lose it on fixation.

8. In fixed material the granules were found to stain with either basic or acid stains.\*
9. The pigment granules did not appear to be either derived from or changed into fat.
10. The pigment granules were not observed to be extruded from the nucleus.
11. There was no evidence that the mitochondria changed into pigment.
12. So far as could be determined from these observations, the granules arise and develop in the cytoplasm of the cell. The first signs of pigmentation were found at the stage of 42 hours' incubation. A few small colorless and small gray granules were seen in the cytoplasm of the cell at this age; these gradually increase in size, number, and depth of color until the cell becomes full of black, rod-shaped granules (17 days). There are at least two stages in the process of pigment production: (a) the formation of a colorless chromogen, followed by (b) the production of color in the chromogen. These processes generally go on simultaneously, but the chromogen may be laid down faster than the coloring takes place. This is shown by the presence of colorless granules in the younger ages.

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## PROCEEDINGS OF SOCIETIES

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

MARCH 1, 1920

#### 1. The Distribution of Adenomyomata Containing Uterine Mucosa.\* DR. THOMAS S. CULLEN.

The following is a short abstract. The paper in full together with illustrations will appear in an early issue of the American Medical Association's new surgical journal—*Archives of Surgery*.

\* Address in Surgery before the Western Surgical Association, Kansas City, Mo., December, 1919, and before The Johns Hopkins Hospital Medical Society, March 1, 1920.

"At the Johns Hopkins Medical Society's meeting in March, 1895, I reported my first case of adenomyoma of the uterus and ever since then have been on the lookout for tumors of this character. From time to time the results of our labors have been recorded either in book form or in the literature.

"I have been amazed at the widespread distribution of these tumors consisting of non-striped muscle with islands of uterine mucosa scattered throughout them.

"Adenomyomata containing uterine mucosa have been found in the following locations: 1. Adenomyomata of the body of the uterus. 2. Adenomyomata of the rectovaginal septum. 3. Adenomyomata of the uterine horn or Fallopian tube. 4. Adenomyomata of the round ligament. 5. Uterine mucosa in the ovary. 6. Adenomyomata of the utero-ovarian ligament.

7. Adenomyomata of the utero-sacral ligament. 8. Adenomyomata of the sigmoid flexure. 9. Adenomyomata of the rectus muscle. 10. Adenomyomata of the umbilicus."

Dr. Cullen after giving briefly the clinical picture and histological findings in cases of adenomyomata of the body of the uterus reported a remarkable case. The right horn of a bicornate uterus was the seat of a widespread and diffuse adenomyoma, the right tube contained a pregnancy, the left tube was the seat of an adenomyoma, and the left ovary had been converted into a large retention cyst.

*Adenomyoma of the Rectovaginal Septum.*—Dr. Cullen laid unusual emphasis on this group of cases and pointed out that many had in the past undoubtedly been overlooked. If left alone the patient in time becomes a chronic invalid or dies as a result of the disease. The clinical picture in adenomyoma of the rectovaginal septum is typical. In the early stages the patient comes complaining of much pain just before or at the beginning of the period and especially on defecation. On bimanual examination a small nodule is felt directly behind the cervix. It cannot at this stage be confused with any other lesion.

Cullen then reported in detail and illustrated ten new cases of adenomyoma of the rectovaginal septum that he had recently personally observed.

*Adenomyoma of the Uterine Horn or Fallopian Tube.*—These growths were next considered and the speaker reported a case in which the tube was 1 cm. in diameter and solid. It consisted of typical adenomyoma.

*Adenomyoma of the Round Ligament.*—Cullen recorded the first case of this variety in the JOHNS HOPKINS HOSPITAL BULLETIN for 1896 and has had several since then. In his most recent paper he refers to a case in which a discrete adenomyoma was found in the round ligament about 2 cm. from the uterine cornua. It contained quantities of typical uterine mucosa.

*Uterine Mucosa in the Ovary.*—Cases published by W. W. Russell, Charles Norris, Dewitt B. Casler and others were discussed, and Cullen referred to some recent cases he had observed in which uterine mucosa was found in the ovary. This abnormal position of uterine mucosa may lead to most unusual clinical symptoms as noted in Casler's case.

*Adenomyomata of the utero-ovarian ligament* are of little clinical significance and are recognized only at operation or in the laboratory.

*Adenomyomata of the uterosacral ligament* are very infrequent and are small. Cullen reported a case that recently came under his care. He diagnosed the condition at operation, removed the adenomyoma and then brought the ends of the uterosacral ligament together again.

*Adenomyomata of the Sigmoid Flexure.*—Cullen records the case of a young woman who had an advanced adenomyoma of the rectovaginal septum. At operation a puckered tumor was found partially encircling the sigmoid near the pelvic brim. It looked like a cancer. On histological examination it proved to be an adenomyoma. The condition is extremely

rare. Cuthbert Lockyer could find the record of only one similar case, that reported by Robert Meyer.

*Adenomyoma in the Left Rectus Muscle.*—Cullen reports a case that had come under the care of Dr. William F. Shallenberger of Atlanta, Ga. An adenomyoma 1.5 x 2.5 cm. was found in the lower end of the left rectus. It presented the typical picture of adenomyoma.

*Adenomyoma of the Umbilicus.*—Cullen briefly mentions this group of tumors and refers the reader to his chapter on this subject in his book on the umbilicus.

*Brief Summary.*—Adenomyomata consisting of a matrix, of non-striped muscle and fibrous tissue with typical uterine mucosa scattered throughout it are to be found in the uterus, rectovaginal septum, tubes, round ligaments, utero-ovarian ligaments, uterosacral ligaments, sigmoid flexure, rectus muscle and umbilicus. Moreover, we occasionally find large quantities of normal uterine mucosa in the ovary. Adenomyomata form one of the most interesting groups of tumors that we have to deal with in the female pelvis.

The paper is of such a nature that it cannot be satisfactorily abstracted. It is accompanied by about fifty original illustrations.

#### DISCUSSION

DR. RICHARDSON.—Every one, I am sure, who is interested in the development of gynecological surgery feels under obligations to Dr. Cullen for having, through his splendid work on adenomyomata, contributed so much of scientific as well as of practical value towards a better understanding of this group of cases about which we formerly knew so little. It has been my good fortune to have seen three cases of adenomyoma of the recto-vaginal septum, and there are one or two clinical points in connection with them which should be emphasized. The first is that the presenting symptom in all of my cases was dysmenorrhoea, a complaint commonly regarded as of secondary importance. But these cases teach us that adenomyoma should be carefully searched for in every case of severe and intractable dysmenorrhoea. My first case was encountered some ten years ago when very little was known about this neoplasm and I did not know the exact nature of the pelvic pathology. The tumor began in the anterior wall of the rectum just back of the cervix and presented all of the characteristics of a small inflammatory area. Conservative surgical measures were employed but, in spite of these, the condition developed progressively and fairly rapidly until it produced a state of chronic invalidism. After some months an effort was made to alleviate the suffering by a hysterectomy and at the operation I found, in addition to the somewhat enlarged uterus, a diffuse distribution throughout the pelvis of a similar inflammatory-looking process formerly seen at its beginning in the anterior rectal wall. The effect of this new growth was absolutely to immobilize the lower portion of the uterus, the broad ligaments and the rectum as if they had been encased in cement. Removal of the uterus was disappointing both as regards inhibition of the process and relief of symptoms. Some months later I was

forced to perform a radical resection of the rectum under tremendous technical difficulties, which resulted in death from surgical shock.

In my other two cases the growth was situated just behind the cervix but had also involved the anterior rectal wall below the peritoneum or culdesac of Douglas. Resection of the rectum in this location is a serious and difficult operation. I decided to advise the use of radium first and if this fails, to resect the bowel before the growth becomes extensive. If operation becomes necessary, as it probably will, preliminary panhysterectomy, as suggested by Dr. Cullen, is the method of choice.

Adenomyoma of the rectovaginal septum is, therefore, a very serious condition; one, indeed, that must be regarded at least as semi-malignant, and which, if let alone, will eventually lead to chronic invalidism and death.

**DR. EMIL NOVAK.**—There are one or two points which I should like to hear Dr. Cullen discuss. In the first place, I have been struck with the relationship which appears to exist between adenomyoma of the uterus and the condition known as hyperplasia of the endometrium. The latter, it may be noted, was also first described by Dr. Cullen, as far back as 1900. In many cases of adenomyoma of the uterus, the mucous membrane, both of the surface of the uterus, and also deep down in the muscular tissue, shows the characteristic pattern of hyperplasia. Even from a clinical point of view these two conditions—hyperplasia and adenomyoma—seem to be related. Both are characterized by excessive menstruation. I have observed a number of cases in which curettage, perhaps repeated several times, has yielded a typical hyperplastic endometrium, and in which subsequent removal of the uterus showed it to be the seat of an unsuspected adenomyoma. The apparent connection between the two conditions suggests various interesting possibilities. Hyperplasia, as the term indicates, is characterized by a genuine increase in both the epithelial and stromal elements of the endometrium. Adenomyoma, in a broad sense, is characterized by a hyperplasia of the muscular elements. Perhaps both conditions are produced by the same underlying cause.

There has been considerable discussion as to the etiology of adenomyoma, especially in the recent German literature. Most of the German authors are inclined to believe that the condition is of inflammatory origin. For example, in a recent article, adenomyoma of the rectovaginal septum is spoken of as adeno-serositis. As regards adenomyoma in general, there seems little ground for this inflammatory theory. While inflammation may cause gland proliferation, it can scarcely explain why the glands in adenomyoma are commonly surrounded by a well-marked mantle of normal endometrial stroma.

I mention these facts merely in an effort to lure Dr. Cullen into a discussion of the cause of this interesting lesion.

**DR. CULLEN.**—The first case Dr. Richardson referred to was a most interesting one. I saw this patient and on open-

ing the abdomen found a uterus about twice the natural size and studded with small myomata. The posterior part of the cervix was firmly adherent to the rectum, and on separation of the two, a raw surface at least 2 to 2.5 cm. in diameter was left on the anterior surface of the rectum. Under ordinary circumstances I would have done a hysterectomy at once, but this patient had recently become engaged and I did not feel at liberty to adopt so radical a procedure without further watching the case. Moreover, at that time we knew absolutely nothing about adenomyoma of the rectovaginal septum.

As you have heard from Dr. Richardson this patient went from bad to worse and finally he had to remove a portion of the rectum.

The development in the adenomyoma in some cases seems to be slow, in others very rapid and the pelvis in time becomes choked with the growth.

Adenomyomata of the rectovaginal septum are at times almost impossible to remove. In one of our cases the ureters ran directly through the adenomyoma. At each period they were markedly constricted, were dilated above the point of obstruction and there was pain in both renal regions due to the damming back of urine. In that case I tunneled the ureters out of the growth, lifted them up and attached them loosely to the sides of the pelvis.

Where it was impossible to remove the entire adenomyoma radium seemed to keep it in check, in at least one instance.

Hyperplasia of the endometrium is a well-defined clinical entity and is a very frequent cause of prolonged and profuse menstrual periods. The histological picture of the endometrium is characteristic. The mucous membrane is thicker than usual. The surface epithelium is intact. Some of the glands are small and round, others large, round or irregular. The gland epithelium is thicker than usual. The stroma is much denser than normal, due to the large increase in the number of stroma cells, and in the nuclei of these cells one frequently finds nuclear figures. The histological picture is definite and cannot be confused with any other pathological condition of the endometrium.

The cause of adenomyoma is unknown. There is no evidence that it is due to an inflammation, as has been suggested by some authorities. The islands of uterine mucosa in the adenomyoma pour out their quota of menstrual blood at the period. This cannot escape; it causes tension in the tumor and undoubtedly irritation, which seems to stimulate further growth.

## 2. Paroxysmal Auricular Fibrillation. DR. VENE R. MASON.

Published in the May, 1920, number of the BULLETIN, page 145.

## DISCUSSION

**DR. HAMMAN.**—There is hardly any clinical condition more dramatic and more interesting than paroxysms of auricular fibrillation. I have observed the condition frequently and yet, whenever I meet it again, this astonishing derangement of cardiac mechanism excites endless wonder and fascination.

I have encountered it especially in two groups of cases. The first group consists of patients past forty years of age with hypertension or myocardial disease. Paroxysms of fibrillation occur with especial frequency at the period when the earliest symptoms of myocardial insufficiency come on and sometimes the advent of fibrillation precipitates the symptoms of myocardial insufficiency. The paroxysms may last from a minute or two to several days or longer. Between the paroxysms the heart may show no evidence of disease or, if hypertension be present, only the changes associated with the high blood pressure. I have seen a number of elderly patients fibrillate transiently during minor disorders such as attacks of diarrhea, and after a number of such transient paroxysms occurring over a period of years finally develop permanent fibrillation.

The second group is made up of otherwise young adults many of them robust and vigorous. The paroxysms of fibrillation come on without any determinable cause and last a varying length of time. Between the attacks the most rigorous examination fails to reveal any cardiac abnormality. After a number of attacks the heart usually fibrillates permanently although it may then continue to fibrillate for years without the development of any symptoms of myocardial insufficiency.

Paroxysms of fibrillation occur in association with other conditions of which perhaps the most important and interesting is disease of the thyroid gland. Although there is little note of it in the literature fibrillation frequently occurs in the late stages of thyroid disease. Permanent fibrillation is sometimes preceded by paroxysms of fibrillation. I have recently observed an interesting instance. The patient complained of attacks of palpitation. Examination revealed the classical symptoms of a large adenoma of the thyroid. I thought the attacks of palpitation were due to attacks of sinus tachycardia until the patient presented herself during an attack when it was obvious that the auricles were fibrillating. The patient refused operation because I was unwilling to promise that removal of the thyroid would prevent the occurrence of further attacks.

DR. CARTER.—Not the least interesting fact in connection with auricular fibrillation is that in spite of all our knowledge of the condition, we really know little concerning the actual cause of the onset of the attack.

In spite of the theories advanced by Rothberger and Winterberg, by Lewis and by Garrey, in explanation of the pathological physiology, that it is due either to a tachysystole, associated with conspicuous shortening in the refractory period of the auricular muscle, or to multiple foci of stimulation, or to the existence of multiple areas of block, no one of these views explains satisfactorily the fundamental cause of the onset of the disturbance, particularly in the transient or paroxysmal form.

In the light of these cases reported by Dr. Mason, and of some of those found in the literature, are we not perhaps justified in believing, from the standpoint of the etiology of its onset, that clinical auricular fibrillation may be divided into

two distinct groups, as has been suggested by Robinson, the one associated with evidence of gross pathological change, the other with changes in the blood supply or in the subtler chemical reactions taking place within the myocardium and not necessarily dependent upon structural change.

The instances of transient or paroxysmal fibrillation occurring in the course of an infection and such cases as those reported by Robinson, following hydrogen sulphide poisoning, would fall into the latter group, while those cases occurring in the presence of myocardial and vascular changes, in many of which hypertension is a conspicuous feature, would fall into the former; though it would be difficult to deny the influence of metabolic changes in these cases also.

Even more difficult to explain satisfactorily are those rare instances of fibrillation occurring in patients under 40 years of age, which remain permanently established, with no evidence of myocardial changes beyond a slight ventricular hypertrophy with a normal cardiac response to effort and with absolutely no symptoms of cardiac distress on the part of the individual. Through the kindness of Dr. Thayer, I have recently seen such an instance in a man of 32, in whom fibrillation had been permanently established for 14 months.

In Dr. Mason's series the age incidence has been high, above 45 or 50, which is what one would expect. In the series reported by Krumbaar, there was one instance of transient fibrillation in a young man of 18.

It is to be hoped that with the advances in our knowledge of cardiac pathological physiology, the elucidation of the etiological factor, especially in relation to these transient and paroxysmal cases, may be cleared up.

MARCH 15, 1920

1. **Cinematograph: Cases of Lethargic Encephalitis.** DR. HENRY M. THOMAS.
2. **Lethargic Encephalitis. Poliomyelitis and Australian X-Disease. (Abstract.)** DR. SIMON FLEXNER.

The world has recently passed through or is now passing through epidemics of at least two diseases, the main effects of which are exerted on the central nervous organs. They are poliomyelitis and lethargic encephalitis. In addition, an epidemic affection of the central nervous system has recently been reported from Australia differing in certain respects from both these afflictions and which for the time being is denominated X-disease. It is my purpose to speak to you of these several diseases and especially to enable you to compare their pathology with one another by means of a series of lantern pictures to be thrown on the screen. It has fortunately been a simple matter to obtain material in this country for lantern slides from cases of poliomyelitis and even from cases of lethargic encephalitis; and I am indebted to Doctor J. B. Cleland of Sydney, Australia, for specimens from the X-disease. Moreover, I have obtained through the British Medical Research Committee specimens from the early cases of lethargic encephalitis arising in England. I am thus enabled to bring together for your observation examples of the

several kinds of epidemic nervous diseases mentioned as they arose in the United States, England and Australia.

In presenting the subject of this lecture to you, I wish to lay stress on the fact that these epidemics of nervous affections are very remarkable, both by reason of their magnitude and their kind, and thus to arouse an interest which through enlarging knowledge may make us safer from their ravages.

It is now clear that the frightful explosion of poliomyelitis which centered in New York State in 1916 can be traced to a series of small outbreaks of the disease in Norway and Sweden that culminated in the relatively severe epidemic of 1905; on the basis of the study of this epidemic Wickman issued his epoch-making book in 1907. It was doubtless this Scandinavian epidemic of 1905 which led to the pandemic of 1906-1907 that spread over Europe, crossed the Atlantic to America, gradually extended over North America, and then passed to South America and the Orient, since which time the disease has prevailed to some extent in the United States and elsewhere every summer and autumn.

Poliomyelitis, even in some degree of epidemicity, was, however, known in the United States previous to 1907. The largest single recorded outbreak prior to 1907 is the epidemic occurring in Vermont in 1894 and reported by Caverly. We get a good notion of the difference between the situation in 1894 and that in 1916 by recalling that the Vermont epidemic included less than 200 cases, whereas in New York State alone in 1916 the recorded cases numbered more than 20,000.

So much, then, for epidemic poliomyelitis by way of introduction to our main theme—lethargic encephalitis. We have seen that it is possible to trace the source of an epidemic or pandemic wave of a given disease. Epidemic poliomyelitis was indeed known in the United States prior to 1907, but no great or widespread epidemic outbreak had ever occurred in this country before that date.

The circumstances are quite different with respect to lethargic encephalitis. There is no history of outbreaks of that affection prior to the present so-called epidemic. Here again, however, by following chronologically the occurrence of the disease in other countries, we can trace the connection of the cases arising in the United States with certain cases which were first recognized in Vienna in the winter of 1916. Moreover, it is now possible to follow the spreading wave of the disease by way of France and England (in which countries cases were recognized in 1918) to the United States where the first cases appeared toward the end of 1918 and in the early months of 1919.

There is now no doubt that the disease which von Economo studied in Vienna in 1916 and to which he gave the name lethargic encephalitis, is identical with the disease to which we are applying that name at the present time. It is now merely of historical interest to recall that both in Austria and in England the disease was misinterpreted and attributed to food poisoning, *i. e.*, botulism, with which condition it has in common the paralysis of the eye muscles. A histological study

of the central nervous system of fatal cases in Austria first, then in England and France, later in the United States and now in many other countries, has brought out profound distinctions from botulism, and provided a pathological-histological basis for the symptomatic and pathological complex now embraced under the denomination of lethargic or epidemic encephalitis.

Of course, the facts regarding the outbreak of 1916 in Vienna were delayed in reaching Western Europe and the United States because of war conditions. Indeed the disease itself, in spite of all barriers, penetrated into England and France in advance of the literature concerning it. But the essential point at present is to recognize that in the United States and doubtless in other western lands an epidemic disease of sinister nature is prevailing for the first time. We are therefore confronted with a condition of present menace and one also of safe-guarding the future so as to prevent, if possible, the establishment of permanent foci in this country.

I said that there is no history of a previous outbreak of encephalitis lethargica in the United States. This does not mean that cases of encephalitis had not been observed before. The point is important since it happens that encephalitis is not an infrequent sequel to epidemic influenza. Because of this association, the question has been raised in various quarters whether after all lethargic encephalitis is not merely a form of post-influenzal encephalitis. I believe that the question can be answered negatively. First, the Viennese outbreak in 1916 antedated the influenza epidemic. Next, no such frequent association of encephalitis with influenza epidemics had been previously noted. Finally, there are pathological differences in the brain in cases of frank post-influenzal encephalitis and cases of lethargic encephalitis, which should not be overlooked. My contention is that for the present and until indubitable evidence is adduced to uphold the notion of a dependent relation of lethargic encephalitis to epidemic influenza, the former should be regarded as an independent disease of infectious and in some degree communicable nature.

I said above that the frequent association of encephalitis with influenza had not been noted in previous epidemics of influenza. This, in my opinion, is a correct statement, it being understood that the word "frequency" has reference to the occurrence of scores and even of hundreds of cases such as have been reported in recent months in the United States alone—and, of course, only a fraction of the cases arising are thus reported or even, possibly, identified. It is a matter of some importance to have this fact quite clearly in one's mind, because in tracing backward the history of afflictions with which lethargic encephalitis may possibly be identified, two instances are frequently quoted—one dating from 1712 and relating to an outbreak of so-called "sleeping sickness" centering about Tübingen in Germany, and the other dating from 1890-1892 and relating to a semi-mysterious disease called "nona" said to have occurred about the borders of Austria and Italy. In both these periods epidemic influenza was raging; hence the suggested connection of one with the other.

On the other hand, it is impossible to form any adequate notion whatever of the nature of the so-called "nona" or indeed to become convinced that a form of "sleeping sickness" actually prevailed at that time in the region mentioned. The references in print are nearly all in the lay press of the day, not in the medical press. Moreover, it is clear that other countries equally attacked by the epidemic influenza of 1889-1892 did not show an unusual number of severe cases of encephalitis.

Accepting for the present that lethargic encephalitis is a clinical entity we may next inquire as to the pathological conditions which signalize it.\* The characteristic appearances are found in the brain and chiefly in the grey matter at the base; they consist of perivascular and interstitial cellular invasions associated with edema and occasional hemorrhages, the latter small and frequently microscopic. The cellular accumulations are mononuclear—made up of lymphocytes, plasma cells and polyblasts with, at times, proliferated glia cells. The lesions seek the grey matter and are most abundant and pronounced about the third ventricle and the Sylvian aqueduct, but they involve the large nuclei below the lateral ventricle, the optic thalamus, the pons and medulla, and even, in some degree, the spinal cord, especially in the cervical part. The cortex is somewhat, but less, affected. The relation of the nuclei of the third, fourth and sixth nerves to the third ventricle and Sylvian aqueduct accounts for the frequency of paralysis of the ocular muscles.

A comparison of the lesions in poliomyelitis and in encephalitis lethargica bring out four essential facts of difference: (1) The location is dissimilar; in poliomyelitis the spinal cord, medulla and pons suffer most. The grey matter located further anteriorly usually escapes and the cortex is infrequently involved. (2) While lymphocytes, plasma cells and even polyblasts occur in the lesions in poliomyelitis, the polymorphonuclear leucocyte plays a more prominent part than in encephalitis. (3) The meninges are far more infiltrated with cells in poliomyelitis, which probably explains the greater changes present in that condition in the cerebrospinal fluid. (4) Finally, in poliomyelitis neuronophagocytosis, in the spinal cord especially, is a very common phenomenon, whereas in encephalitis it is met with only infrequently.

We have therefore in poliomyelitis and lethargic encephalitis two definite pathological conditions affecting chiefly the brain and spinal cord with which the symptoms in each instance can be correlated. The two diseases are obviously distinct pathologically, and as experiment has shown, are distinguishable etiologically. Poliomyelitis is readily transmissible to monkeys through inoculation with the affected central nervous tissues; lethargic encephalitis is either not transmissible at all or only rarely and with difficulty.

There is a third epidemic disease of the central nervous organs of which our information is recent and, at the moment, rather meagre. But it is of great interest to ascertain whether

\* All the points mentioned in connection with the pathological histology were illustrated with lantern slides.

this third disease belongs to one or the other category we have been discussing, or is an independent affection. The point is not merely academic. It is a serious enough circumstance to have two severe and highly fatal epidemic diseases of the central nervous system flourishing extensively at the present time. We should be cautious therefore before adding to the list of these enemies of mankind.

This third affection comes to us under the name of Australian X-disease. It has been described in detail by Doctor J. B. Cleland \* who has kindly sent me tissues from fatal cases in man and from inoculated animals. It prevailed in parts of New South Wales, Victoria and Queensland in 1917 and 1918 and was highly fatal. Several hundred cases were reported. At first the disease was regarded as epidemic poliomyelitis, but most of the cases did not show the usual spinal cord involvement, and few instances of typical and frank flaccid paralysis of the extremities were noted. The age distribution of cases resembles that of poliomyelitis; the mortality (70 per cent) is far higher than in that disease, but the seasonal incidence is the same—namely, late summer and early autumn (the month period being, of course, reversed in the southern hemisphere) while lethargic encephalitis has thus far prevailed in the winter period.

The pathological changes in the spinal cord in Australian X-disease resemble those of epidemic poliomyelitis. Cellular infiltration of blood vessels, of the interstitial tissues and neuronophagocytosis are striking. The monkey is readily infected by inoculation with the affected nervous organs of man. So far, then, there is similarity between Australian X-disease and poliomyelitis. But whereas no one has succeeded in communicating poliomyelitis to sheep, calves and the horse by inoculation, Cleland believes that he has infected those animals with Australian X-disease. This is a very important distinction; and this ready communicability of Australian X-disease to animals distinguishes it not only from poliomyelitis but notably also from encephalitis.

I have been enabled, as I said, to study tissues from Australian X-disease in man, monkey, sheep, calf and horse. The lesions in the nervous tissues in man and the monkey are similar to those of poliomyelitis in man and monkey. There is no analogy in poliomyelitis with the lesions in the other animals. Brain tissues, not spinal cord of the other animals, were sent me by Doctor Cleland. They show mononuclear cell invasion of the meninges and focally of blood vessels in the cortex, and a certain extrusion of similar cells in the grey matter about the affected vessels. The evidences then of a meningoencephalitis of mononuclear variety are convincing.

There is one question which might be raised regarding the results of the experimental inoculations, namely, whether in the infection of the sheep, calf and horse (the inoculations were made from the infected monkeys) a second and extraneous

\* Cleland, J. B., and Campbell, A. W., Acute encephalo-myelitis. A clinical and experimental investigation of an Australian epidemic., *Brit. Med. Jour.*, May 31, 1919, page 663.

ous pathogenic microorganism might have been accidentally introduced. I do not emphasize this point, which is to be regarded as a mere possibility, in the endeavor to correlate the findings in Australia with those elsewhere in the world and to exercise due caution and restraint before accepting as certain the existence of a third active epidemic disease of the central nervous system. There are other ways to approach this matter in the effort to clear up the subject, namely, through cross inoculation tests in recovered monkeys with poliomyelitis material, serum immunization experiments, etc. All this will doubtless be attempted in time.

To conclude: I regard epidemic poliomyelitis as a disease with a special pathologic anatomical foundation in the central nervous organs and a specific inciting microorganism. I regard as probable that lethargic encephalitis will be found to occupy a similar special category; while I am inclined to reserve judgment respecting Australian X-disease, which I think may possibly be discovered to be a somewhat special instance of epidemic poliomyelitis in which the brain rather than the spinal cord has had to stand the greater shock of attack.

#### DISCUSSION

**DR. BARKER.**—I would like to ask whether, as we look back with the knowledge we now have of the disease, enough has been discovered about it to permit us, if we were starting over again in 1907, to prevent its development? Is there any lesson to be drawn concerning the prevalence of lethargic encephalitis?

**DR. FLEXNER.**—Dr. Barker's question is not an easy one to answer. No one, I think, can say just what might have happened had we, that is, the medical profession in general, been better informed regarding epidemic poliomyelitis in 1907. Wickman's remarkable book, based on the Swedish epidemic of 1905, appeared in German in 1907. He described the abortive type of case and laid on it great stress as a factor in disseminating the disease. Knowledge and appreciation of this fact were slow in making progress in this country. It is a matter of some national pride that actually Caverly first apprehended the abortive type of poliomyelitis during the Vermont epidemic of 1894.

Let us suppose for the moment that Wickman's book had become widely known in 1907 and the next subsequent years, that the medical profession had been alert about the abortive cases, and especially that suitable and adequate measures of control had been applied. It is by no means certain, of course, that the later outbreaks of poliomyelitis would have been certainly prevented; it is equally by no means certain that their extent and severity might not have been mitigated. In questioning the value of general preventive measures, we are of course putting on trial some of the most common of our public health procedures to limit the spread of the infectious diseases communicated by personal contact. Until other and more direct means of control are secured, we are still dependent on measures based on personal hygiene to combat a whole group of communicable diseases and especially those in which the mode of infection is by way of the upper respiratory mucous membrane, among which poliomyelitis is to be placed and not improbably lethargic encephalitis also.

#### NOTES ON NEW BOOKS

*The Blind.* By HARVEY BEST. Cloth, \$4.00. (New York: The Macmillan Company, 1919.)

In this monumental work by Dr. Harvey Best, Professor of Sociology at the University of Kentucky, two important subjects are fully dealt with—the prevention of blindness and the economic condition of the blind.

Approximately 64 per cent, or nearly two-thirds, of the blindness in the United States, so the author estimates, is preventable. Of specific diseases of the eye likely to cause blindness, the most important are, in the order of their seriousness, cataract, atrophy of the optic nerve, glaucoma, ophthalmia neonatorum, trachoma, and corneal ulcer. Of these diseases, ophthalmia neonatorum and trachoma are under ready control, the disease being preventable in babies by means of the Credé method. To fight trachoma, seven hospitals have been established in the country—three in Kentucky, and one each in Virginia, Tennessee, West Virginia, and North Dakota. Two other infectious eye diseases, keratitis and conjunctivitis, may be checked by comparatively simple precautions. As for the large amount of blindness which is a concomitant of old age, or that which arises from apparently unavoidable diseases, there would be a substantial lessening if good lighting arrangements and saner modes of life were adopted.

Diseases other than specific affections of the eye cause 9.2 per cent of all blindness, the greatest offenders being, in order, measles, meningitis, scarlet fever, smallpox, typhoid fever, and

influenza. In these cases careful attention and isolation will reduce the incidence of blindness.

Accidents especially from explosives cause 13.5 per cent of blindness. Almost all of these may be prevented by care and proper safeguards, such as goggles for men working at dangerous operations in factories and contrivances like guards on emery wheels and exhaust systems to carry off dust and sharp particles in factories.

Although, according to Best's statistics, 46 per cent of blindness cannot be definitely accounted for, being reported as congenital or due to catarrh, colds, or sore or strained eyes, most of these cases also, too, seem to be preventable, since apparently they are largely due to diseases mentioned above.

As for the economic condition of the blind, statistics from census reports seem to show that only about 6.6 per cent are able to make an independent living, four-fifths of those gainfully employed earning a sum below \$500, nearly two-thirds below \$300, more than one-half below \$200 and nearly one-third below \$100, many being subsidized by what are known as pensions, which amount to an average maximum of \$250 a year. It is no wonder, then, that the cost of blindness amounts to the enormous sum of \$30,725,000 yearly.

The question now arises, "Cannot the blind be so trained that most of them may be able to make an independent livelihood?"

The first essential to such an end is that the public should be aroused to the possibilities of blind labor. Instead of looking on the blind man as helpless, instead of taking the pencil-selling beggar as the type, the public must realize that the blind man wants opportunity, not sympathy or charity.

The second essential is that the blind man should be properly and thoroughly trained in an industrial, commercial or professional occupation. In this connection, a paragraph from "Charities and the Commons" is interesting, although not entirely fair:

"Many of the States have been generous in their provision for the education of the young blind. . . . At the close of the school period of their lives, however, at the most critical juncture, when their whole future is to be determined, intelligent interest seems suddenly to cease. . . . (the blind) have outgrown the school and we have no place for them in the active world. . . . They have no business training. Many of them have no profession, most of them have no trade."

The most salient fact with reference to the welfare of the blind is that their opportunities for vocational training are limited. Yet of all classes they need such training the most. To provide it, there are only the workshop and summer sessions in a few of the schools for youth. There is no higher institution of an exclusively educational nature open to blind adults, where they may be trained, as they must be, if they are to be capable workers in trade, industry, or profession.

Add to this fact the further fact that about half the blind children of the country, between the ages of five and nineteen, are not attending any school, and one needs not wonder why the blind man is looked upon as incapable. The fault for such poor attendance does not lie with the schools, because workers for the blind are more than zealous in urging parents to send their children to school. The fault rather lies in the fact that compulsory education laws are not rigidly enforced.

Throughout the book Mr. Best evinces thorough study and careful analysis of his material. He began the work in 1908, finishing in 1919, after examining hundreds of books, pamphlets, manuscripts, reports, statutes, and letters. His work is authoritative and appears at a critical time when interest in the blind and in the possibilities of labor for the handicapped is at its highest flood.

The several bibliographies are comprehensive, thorough and up to date.

J. B., JR.

*Manual of Psychiatry.* Edited by AARON J. ROSANOFF, M.D., Clinical Director, King's Park State Hospital, N. Y., Lieutenant Colonel, Officers' Section, Medical Reserve Corps, U. S. Army. Fifth edition. Revised and enlarged. Cloth. 684 pages. (New York: John Wiley & Sons, Inc. London: Chapman & Hall, Limited, 1920.)

The fifth edition of de Fursac's Manual of Psychiatry appears now as Manual of Psychiatry, edited by Rosanoff, with de Fursac, Rosanoff, Hollingworth, Miss Jarrett and Neymann as contributors. It is no longer merely the French rendering of German psychiatry with some American annotations. The annotations have become a more and more important part of the book and they consist not only of numerous new chapters, but of many transformations of the original. Rosanoff has incorporated Neymann's technique of the spinal fluid study, Meyer's outline of aphasia study, the development of the child, the Terman revision of the Binet-Simon scale (including the average and the superior adult), Kent-Rosanoff's free association test with the frequency-tables and a grouping of the results, group tests, the classification of mental diseases adopted by the American Medico-Psychological Association, with G. H. Kirby's definitions and explanatory notes—altogether a very valuable collection of information. The 120 pages on the practice of psychiatry give a

very valuable summary of the methods in use in modern American psychiatry.

Constitutional disorders, alcoholic, drug and syphilitic disorders and miscellaneous groups supply the nosological headings.

Cerebral arteriosclerosis appears as Chapter XV under "Syphilitic Disorders."

In the discussion of the psychoneuroses, Rosanoff gives considerable attention to the war experience.

The student will find the book of considerable help for reviews and for reference.

*The Principles of Anatomy as Seen in the Hand.* By FREDERIC WOOD JONES, D.Sc., M.B., B.S. Cloth, \$5.00 net. (Philadelphia: P. Blakiston's Son & Co., 1920.)

This is that rare thing, a continuously readable book on gross anatomy,—interesting because it deals with ideas instead of cataloguing bare facts, and none the less instructive because those principles which the author has chosen for exposition are in some part not those which awake most attention in our schools.

It is to be hoped that the newer methods now at work in our dissecting rooms may at length give us American publications of this type, which will show those who know gross anatomy only through the older text-books what stores of interest and utility there are in the anatomy of function as studied by the three methods of embryology, histogenesis, and especially physiology. A fourth source of aid in rationalizing the vastly numerous details of human structure, comparative anatomy, most of us have esteemed less valuable for teaching and practice, but of late we have seen our British colleagues make clever use of it. One Australian comparative anatomist (W. Colin M'Kenzie) has made even so seemingly remote a subject as the musculature of the marsupials do him good service as the foundation of practice in military orthopedics and of an illuminating work on "The Action of Muscles."

In "The Principles of Anatomy as Seen in the Hand" F. Wood Jones has likewise undertaken to show us how the details of structure may be made living and useful by comparison with other species and by a study of the gross physiology. His clear and lively teaching of anatomy from these aspects is founded upon sure knowledge; it is only when lessons are to be drawn from general physiology and embryology that the text wanes in vigor.

The opening chapters deal with the bones of the hand and wrist in a manner far more interesting than this subject traditionally assumes. In the chapter upon "Flexure Lines" there is solid information and also some good scientific jesting when the author examines the lore of palmistry in the light of comparative anatomy. A chapter on the fascias is a triumph of common sense, which every dissector should read as an antidote to the usual text-book description of fascias as square-edged walls of sheet-iron texture. The accounts of the general action of muscles and the position of rest are also sound applications of gross physiology, teaching the structures as they work, not merely as they look.

The chapters on the morphology and the detailed actions of the muscles are the surest of the book, for here the author is upon the ground of his own researches, and has much to teach the clinician and the anatomist. The student may be dismayed to find the subject of muscle-actions, as presented here, far more intricate than in the text-books, but he will also find it, for once, a live subject worth the exercise of good cortical substance, no longer a mere test of memory.

Much space is given to the thesis already enthusiastically expounded in an earlier book of the author ("Arboreal Man"),

that the fore-limb of man is not, as anatomists long taught and theologians repeated, the result of high specialization, but that, on the contrary, it retains to an astonishing degree the generalized structure of the vertebrate type. When the limb is specialized, its freedom is lost, as in the human foot and the fore-limbs of the hooved mammals. Retention of versatile simplicity, with greater control, gives man his adaptable fore-limb, according to the thought-provoking notion of our author.

Discussions of the nerves of the hand, of the hand as a sense-organ, and of the relations of hand and brain, are careful and clear, but less original than the foregoing parts of the book. In the chapter on the vascular channels the author seems least at home, for he has not grasped the opportunity to base his account upon the principles of vascular development, which embryological studies have brought out in recent years. A brief discussion of generalities about the lymphatic system rests dogmatically upon one side of this actively controverted question. It is surely unsafe to think of the lymphatic ducts as phylogenetically earlier than the blood-vessels.

The book is written throughout in a very clear and easy style. There are numerous historical allusions and quotations, many of them from out-of-the-way sources, which are appropriately used in the interest of lucidity.

G. W. C.

*Introduction to General Physiology.* By W. M. Bayliss, M.A., D.Sc., F.R.S. Cloth, \$2.50 net. (London: Longmans, Green & Co., 1919.)

Those who are already acquainted with Bayliss' contributions to the science of physiology will be ready to accept this small book without explanation. It is designed primarily, as the title indicates, for first studies of the subject and is a worthy successor to its forerunners written by Huxley and Martin.

The style is simple and succinct, with frequent helpful analogies to facilitate comprehension of the problems under discussion. The opening chapter surveys the newer work in physics and chemistry which has exerted so profound an influence on modern physiology. Then follow chapters on the several functional processes of the body considered from the standpoint of mammalian physiology. At the end of the book a series of experiments, correlated with the text, is given, which are adapted to laboratory exercises. Throughout the text frequent reference is made to the author's "Principles of General Physiology," thus providing access to a wider discussion for those who desire it.

The book should prove of very great value to those who are responsible for elementary courses in physiology. To others, and particularly to physicians who have of necessity lost touch with the later developments in the laboratory subjects, it will prove a pleasant means for review of the salient facts as seen by one of the most eminent physiologists of the day.

D. H.

## BOOKS RECEIVED

*John Coakley Lettson and the Foundation of the Medical Society.* Being the Presidential Address Delivered Before the Medical Society of London on October 8, 1917, by Sir St. Clair Thomson, M.D., F.R.C.P. Lond., F.R.C.S. Eng. 1918. 8°. 63 pages. Harrison & Sons, London.

*The Rockefeller Foundation. Review for 1918.* Public Health in Many Lands. Centers of Medical Education. War Relief and Welfare of American Troops. By George E. Vincent. 1919. 8°. 40 pages. New York.

*The Rockefeller Foundation. China Medical Board.* Third Annual Report January 1, 1917–December 31, 1917. 1918. 8°. 29 pages. New York, N.Y.

*Smithsonian Institution.* Annual Report of the Board of Regents Showing the Operations, Expenditures, and Condition of the Institution for the Year Ending June 30, 1915. 1916. 8°. 544 pages. Government Printing Office, Washington.

*Industrial Nursing.* For Industrial, Public Health, and Pupil Nurses, and for Employers of Labor. By Florence Swift Wright. R.N. 1919. 12°. 179 pages. The Macmillan Company, New York.

*Cerebrospinal Fluid in Health and in Disease.* By Abraham Levinson, B.S., M.D. With a foreword by Ludvig Hechtken, M.D. With fifty-six illustrations, including five color plates. 1919. 8°. 231 pages. C. V. Mosby Company, St. Louis.

*Psychiatric-Neurologic Examination Methods.* With Special Reference to the Significance of Signs and Symptoms. By Dr. August Wimmer. Authorized translation by Andrew W. Hoisholt, M.D. 1919. 8°. 177 pages. C. V. Mosby Company, St. Louis.

*Collected Papers from The Research Laboratory Parke, Davis & Co., Detroit, Mich.* Dr. E. M. Houghton, Director. Reprints. Volume 6. 1919. 8°. 303 pages.

*Connecticut State Medical Society.* Proceedings of the 127th Annual Convention. Editor James Frederick Rogers. 1919. 8°. 296 pages. Published by the Society, New Haven, Connecticut.

*Metropolitan Asylums Board.* Annual Report for the year 1918. (21st year of issue.) 1919. 8°. 64 pages. Henderson & Spalding, Ltd., London.

*Plastic Surgery, its Principles and Practice.* By John Staige Davis, Ph.B., M.D., F.A.C.S. With 864 illustrations containing 1637 figures. 1919. 8°. 770 pages. P. Blakiston's Son & Co., Philadelphia.

*American-Hellenic Society.* Reports of the American Red Cross Commissions upon their activities in Macedonia, Thrace, Bulgaria, the Aegean Islands and Greece 1919. 8°. 30 pages. Published by permission of the American Red Cross for the American-Hellenic Society, by The Oxford University Press, American Branch, New York City.

*State of Iowa.* Eleventh Biennial Report of the Board of Control of Institutions for the period ending June 30, 1918. 8°. 354 pages. Published by the State of Iowa, Des Moines.

*The Medical Treatment of Cancer.* By L. Duncan Bulkley, A.M., M.D. 1919. 12°. 386 pages. F. A. Davis Company, Philadelphia.

*Atlas of Operative Gynaecology.* By Barton Cooke Hirst, M.D. 164 plates; 46 figures. 1919. 4°. 292 pages. J. B. Lippincott Company, Philadelphia and London.

*Vicious Circles in Disease.* By Jamieson B. Hurry, M.A., M.D. (Cantab.). With illustrations. Third and enlarged edition. 1919. 8°. 377 pages. P. Blakiston's Son & Co., Philadelphia.

*Modern Dentistry for the Laity.* Industrial Dentistry for the Corporation, Modern Preventive Dentistry and Industrial Welfare Dentistry. By Alfred A. Croker. Second edition. 1919. 12°. 136 pages. The Dental Register, Cincinnati, Ohio.

- Thoughts of a Psychiatrist on the War and After.* By William A. White, M. D. 1919. 12°. 137 pages. Paul B. Hoeber, New York.
- Half a Century of Small-Pox and Vaccination.* Being the Milroy Lectures delivered before the Royal College of Physicians of London on March 13, 18 and 20, 1919. By John C. McVail, M. D., LL. D. 1919. 8°. 86 pages. E. & S. Livingstone, Edinburgh.
- Organization of Public Health Nursing.* By Annie M. Brainard. 1919. 12°. 144 pages. The Macmillan Company, New York.
- The Exact Diagnosis of Latent Cancer.* An Enquiry into the True Significance of the Morphological Changes in the Blood. By O. C. Gruner, M. D. 1919. 8°. 79 pages. P. Blakiston's Son & Co., Philadelphia.
- Report of the Scientific Work of the Surgical Staff of the Woman's Hospital in the State of New York.* Edited by George Gray Ward, Jr., M. D., F. A. C. S. Volume II. 1919. 8°. 234 pages.
- The Proceedings of the Charaka Club.* Volume V. 1919. 8°. 101 pages. Paul B. Hoeber, New York.
- The Venereal Diseases.* An Outline of Their Management, Prepared Under the Surgeon General of the Army for the Use of Medical Officers. Revised for the use of civilian physicians. Third edition. Printed for the United States Public Health Service, Rupert Blue, Surgeon General. 1919. 24°. 159 pages. American Medical Association, Chicago.
- Bacteriology in Abstract.* By A. B. Wallgren, B. S., M. D. 1919. 24°. 340 pages. Medical Abstract Publishing Company, Pittsburgh, Pa.
- A *Text-Book of Human Physiology.* Including a Section on Physiologic Apparatus. By Albert P. Brubaker, A. M., M. D., LL. D. Sixth edition, revised and enlarged with 356 illustrations. 1919. 8°. 794 pages. P. Blakiston's Son & Co., Philadelphia.
- A *Text-Book Upon the Pathogenic Bacteria and Protozoa.* For Students of Medicine and Physicians. By Joseph McFarland, M. D., Sc. D. Ninth edition, revised with 330 illustrations, a number in colors. 1919. 8°. 858 pages. W. B. Saunders Company, Philadelphia and London.
- College of Physicians of Philadelphia.* Transactions. Third Series. Volume the Fortieth, 1918. 8°. 308 pages. Printed for the College, Philadelphia.
- Yearbook of the United States Department of Agriculture,* 1918. 8°. 760 pages. 1919. Government Printing Office, Washington.
- American Association for the Study and Prevention of Infant Mortality now the American Child Hygiene Association.* Transactions of the ninth annual meeting, Chicago, December 5-7, 1918. Part I—Proceedings of the Session on Child Welfare. 1919. 8°. 354 pages. Franklin Printing Company, Baltimore.
- Bulletin of Iowa Institutions.* (Under the Board of Control) Published Quarterly. Volume XX. 1918. 8°. 261 pages.
- The Carnegie Foundation for the Advancement of Teaching.* Justice and the Poor. By Reginald Heber Smith. Bulletin Number Thirteen. 1919. 8°. 271 pages. New York City.
- Carnegie Endowment for International Peace.* Founded December Fourteenth, Nineteen Hundred and Ten. Year Book. No. 8. 1919. 8°. 209 pages. Washington, D. C.
- Quarterly Medical Clinics.* A Series of Consecutive Clinical Demonstrations and Lectures. By Frank Smithies, M. D. Volume I. Number 2. April, 1919. 8°. Medicine and Surgery Publishing Company, Inc., St. Louis.
- Publications of the South African Institute for Medical Research.* Edited by W. Watkins-Pitchford, M. D. (Lond.) No. XII. Observations and Experimental Investigations in Epidemic Influenza. By F. S. Lister, M. R. C. S., L. B. C. P., and E. Taylor, M. D. (G. W. Univ., U. S. A.) 1919. 8°. 23 pages. Hortors, Limited, Johannesburg.
- Pellagra.* By H. F. Harris, M. D. 1919. 8°. 421 pages. The Macmillan Company, New York.
- Experimental Pharmacology.* By Hugh McGuigan, Ph. D., M. D. Illustrated with 56 engravings and 7 colored plates. 1919. 8°. 251 pages. Lea & Febiger, Philadelphia and New York.
- The Prevention of Dental Caries and Oral Sepsis.* By H. P. Pickrell, M. D. Second edition. 1919. 8°. 374 pages. Paul B. Hoeber, New York.
- Nervous and Mental Diseases.* By Archibald Church, M. D., and Frederick Peterson, M. D. Ninth edition, thoroughly revised. With 350 illustrations. 1919. 8°. 949 pages. W. B. Saunders Company, Philadelphia and London.
- Manual of Obstetrics.* By Edward P. Davis, A. M., M. D., F. A. C. S. Second edition, revised. 1919. 12°. 478 pages. W. B. Saunders Company, Philadelphia and London.
- Spanish Tales.* For Beginners. Edited with notes and vocabulary by Elijah Clarence Hills, Ph. D., Litt. D. Revised edition with direct method exercises. 1919. 16°. 298 pages. Henry Holt and Company, New York.
- Oxford Medical Publications.* Publishers: Henry Frowde, London; Hodder & Stoughton, London. The following 10 volumes:
- The Medical and Surgical Aspects of Aviation.* By H. Graeme Anderson, M. B., Ch. B., F. R. C. S. With chapters on *Applied Physiology of Aviation.* By Martin Flack, M. A., M. B., and *The Aero-Neuroses of War Pilots.* By Oliver H. Gotch, M. B., Ch. B., M. R. C. P. (London) and an introduction by the Right Hon. Weir, of Eastwood, P. C. 1919. 8°. 255 pages.
- Trench Fever, a Louse-Borne Disease.* By Major W. Byam, R. A. M. C.; Captains J. H. Carroll, U. S. R., J. H. Churchill, R. A. M. C. (T.), Lyn Dimond, R. A. M. C., V. E. Sorapure, R. A. M. C., R. M. Wilson, R. J. M. C., and L. L. Lloyd, R. A. M. C. (T.). With an introduction by Lieut-General Sir T. H. Goodwin, K. C. B. A foreword by Major-General Sir David Bruce, K. C. B., F. R. S., A. M. S., and a summary of the report of the American Trench Fever Commission by Lieut. R. H. Vercoe, R. A. M. C. 1919. 8°. 196 pages.
- The Nervous Heart, Its Nature, Causation, Prognosis and Treatment.* By R. M. Wilson, Captain, R. A. M. C., and John H. Carroll, Major, M. C., U. S. A. 1919. 16°. 136 pages.
- Psychoses of the War, Including Neuroasthenia and Shell Shock.* By H. C. Marr, Lt.-Col., R. A. M. C. (Temp.). 1919. 8°. 292 pages.
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Public Service

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Honor of His Seventieth Birthday and First  
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## CAPILLARY POISONS AND SHOCK<sup>1</sup>

By H. H. DALE

(From the Lister Institute of Preventive Medicine, London, England)

May I begin by expressing my very deep sense of the honor which has been done to me in the invitation to deliver the Herter lectures in this world famous university? I can conceive for no worker in science a greater honor, or a keener pleasure, than that afforded by such a request to come from afar and talk about his own work, his own ideas, hopes and failures, with those from whom he has hitherto drawn inspiration and encouragement, whose scientific fellowship he has hitherto been able to enjoy, mainly through the printed, or, at best, the written word.

For myself, I have found in this invitation, not only pleasure and gratification, though these in abundance, but a measure of embarrassment. In the case of any one of the distinguished men who have preceded me in this lectureship, it would not be difficult to point to one or more fields of investigation in which his work had conspicuously aided progress, with which, in the terms attached to Dr. and Mrs. Herter's noble gift, he had himself been identified. Any one in touch with the progress of medical science would know what the Selection Committee had in mind, what they expected from the lecturer, when the invitation was given. Looking back over the past 15 years, I have been bound to admit that I can trace in my own case no consistent devotion to any line of work. I seem to have been drawn into a number of ap-

parently disconnected investigations by curiosity, the accident of routine, above all, by the happiness of association with a small company of brilliant and enthusiastic colleagues. The only real link of connection seems to have been at the common starting point of these joint expeditions, which was curiously remote from most of our ultimate destinations.

The starting point has an interest more personal than scientific, and I allow myself the egotism of allusion to it, partly to provide myself now, as then, with a point of departure, but more especially to enable me to pay a passing tribute to the broadminded policy which enabled my colleagues and myself, in circumstances where many would not expect such freedom, for years to follow the lead of purely scientific interest, unhampered by considerations of immediate practical outcome. Dr. Barger and I were asked in 1904 to undertake an investigation of the chemistry and pharmacology of ergot. We determined to take, one by one, any characteristic forms of physiological activity which I could detect in the substance and its extracts, and to use each in turn as a guide to the chemical isolation and identification of the substance producing it. We believed the problem to be a difficult one, but it proved to have a complexity and an interest altogether beyond our expectation. It was our great good fortune to find in ergot a veritable treasure house of substances, presenting, in intense degrees, the most varied forms of pharmacological activity and in the study of these, my colleagues and

<sup>1</sup> Lecture I of the Herter Series delivered before The Johns Hopkins University, November 13, 1919.

I wandered far from the immediate problem of the therapeutic action of ergot, into an investigation of the epinephrine type of action and its relation to the effects on true sympathetic nerves of the muscarine type of action and its relation to the effects on other nerves of the autonomic system; and into a study of the effects of substances producing a shock-like depression of the circulation, similar to that encountered in a large class of pathological conditions. It is to an analysis of this last-mentioned, curious and, as I believe, significant type of action, that I desire to ask attention to.<sup>1</sup> In a second lecture I hope to deal with a special example in the so-called anaphylactic shock. In a third lecture I shall endeavor, by a transition which, as I hope to convince you, is less forced and abrupt than might appear, to pass from the anaphylactic phenomena to a more general consideration of the connection between chemical structure and physiological action, as illustrated by the action of certain groups of substances related to the other active constituents of ergot. For the present I invite your attention to a shock-like effect on the circulation and other vital activities.

We had long known that ergot extracts exhibited a direct and intense stimulant action on plain muscle, and, in particular, on the plain muscle of the uterus. None of the principles which we had hitherto identified would account satisfactorily for this action, which, on the face of it, seemed to be more directly related to the therapeutic use of the drug than the other types of activity which we had described, length, after many methods had been tried in vain, Barger succeeded, by using Kutscher's method of separating the substances as the organic bases in meat extract, in isolating a base from ergot which produced this action with an ordinary intensity. One part of this base in 100 millionths of a solution had still a pronounced effect on the tone of uterine muscle. It proved to be one of the series of amines formed by decarboxylation of amino-acids. In this instance the parent amino-acid was histidine, and the identification of the base was greatly facilitated by the fact that Ackermann almost simultaneously, produced it from histidine by the action of bacteria. General usage has conveniently and appropriately named it "histamine." The interest of this substance, however, was by no means limited to its occurrence and contribution to the activity of ergot. The significance of its action began to appear only when its physiological effects came to be more closely analyzed, and the investigation has led us far, indeed, from our original objective. Laidlaw and I began to examine the action of this substance more closely, we soon recognized that it produced, in relatively minute dosage, a type of effect long familiar, though incompletely understood. This type of action had hitherto been identified with the action of certain products of partial cleavage of proteins, such as the familiar W-peptone, certain protamines and histones, and the products of gentle alkaline hydrolysis obtained by Vaughan and his colleagues. It was, perhaps, of special interest that an example of this general type had been demonstrated with extracts of a large number of different organs of the animal body.

ski had postulated the presence in all such extracts and hydrolytic products of a hypothetical principle, "vasodilator." Just before we began to examine the action of histamine, this type of action had acquired a new and absorbing interest from the fact that it was found to be faithfully reproduced in, to constitute, indeed, the complex of symptoms known as the anaphylactic shock, even to the details of variation which that phenomenon showed in the different species. So that, within a single year, this same complex of symptoms, hitherto known as the effect of products of protein digestion and of organ extracts, was found to be reproduced in the reaction of a specifically sensitized animal to a normally inert protein, and in the action of a pure base, obtainable by a relatively simple change from one of the amino-acids out of which the protein molecule is built.

I need hardly indicate the temptation which was presented to any one coming upon these facts for the first time. I have mentioned Popielski's view that the various organ extracts and crude products of digestion owed their common type of activity to the presence, in varying proportions, of a single active substance. The idea that the anaphylactic phenomena were due to the production in the circulation of a substance of this type, by the action of a specific ferment, was already in the air. The suggestion lay near at hand that the long-sought active substance was "histamine," and that the production of the latter in the system was the cause of the anaphylactic shock. The temptation to make such a suggestion was even accentuated, when Barger and I were able to show that in one particular organ extract, that from the intestinal mucosa, histamine was actually present. The suggestion, however, was not made by us, though others were not slow to make it for us, and even to attribute to us the view that the anaphylactic shock was due to the liberation of histamine. The presence of histamine in extracts of other tissues than the intestinal mucous membrane, remained for us a highly speculative possibility; as for the anaphylactic shock, my own observations soon led me to a conception of this phenomenon in which histamine played no direct part, and which I shall endeavor to explain to you in my next lecture.

It may be that the event will prove us to have been too cautious. You will be familiar with the highly suggestive experiments recently carried out here by your own distinguished Professor of Pharmacology, Dr. Abel, in association with Dr. Kubota. These experiments have again placed in the center of interest for all workers in this field the possibility that histamine itself, or some compound or derivative of histamine, may be the active constituent in the different impure cleavage-products and organ extracts which have this type of action. Dr. Abel would not expect or value from me the empty compliment of an assumption that he has completed a proof towards which his work has made a beginning brilliant with promise. If he succeeds in proving that histamine itself, or some recognizable derivative, is split off from protein in hydrolysis, or from tissues in death or early autolysis, he will have built a firm structure where my colleagues

and I have merely sketched a vague outline and none will rejoice more sincerely than we.

Meanwhile, he will understand my desire to leave this chemical aspect of the question open, and to direct your attention to the nature and significance of the type of physiological action, which the discovery of the action of histamine enabled us to investigate.

If our study of this symptom-complex, produced by histamine or any of these protein derivatives, had been carried out with impure extracts or complex products of digestion, we should probably have been led to assume that more than one active principle was at work, especially in producing the effects on the circulation; for the action on certain species might easily suggest a conflict of opponent actions. The discovery of all these various and, in some ways, apparently conflicting effects in the action of the one pure substance, histamine, cleared our minds of any suggestion of a multiplicity of principles, but left us faced with a paradox, which for years has held our interest, and until quite recently has baffled all attempts at explanation. It can be stated in a few words. Histamine, and the group of protein derivatives having a generally similar type of action, have a powerful stimulant effect on the tone of all plain muscle. Not merely the uterine muscle, the action on which first came to light, but the muscular coats of the bowel, the bronchi and of the arteries are stimulated to strong tonus. If the blood vessels of any organ, from any animal, are perfused artificially with blood or Ringer's solution, histamine, added in any effective dose to the perfusion fluid, causes pronounced contraction of the arteries, as shown by retardation of the flow of fluid and shrinkage of the organ. The same stimulation of tone by histamine is observed in a strip of arterial wall suspended in Ringer's solution, as several observers using arteries from different species and different parts of the system, have shown here in Professor Abel's laboratory. Now in some species, such as the rabbit, this effect is visibly reproduced *in vivo*, a small dose of histamine, under conditions eliminating complication from effects on the pulmonary circulation, causing a simple rise of arterial blood-pressure by vasoconstriction; in other species, however—in the carnivora, in the monkey, probably in man—the effect of a small dose of histamine, injected into the living circulation, appeared to be the exact opposite of this. A fall of arterial blood-pressure was the invariable result, and the most careful analysis of this, by means of the plethysmograph and the cardiometer, as well as by simple inspection of exposed organs, left no escape from the conclusion that this fall of blood-pressure was due to vasodilatation, to a general weakening of the peripheral resistance, and not to diminished output from the heart, or to obstruction of the blood-flow through the liver, as Mautner and Pick suggested. In these species, therefore, we had the most complete apparent contrast between a vasoconstrictor effect of histamine, increasing the resistance to the blood-flow through an artificially perfused organ, and a vasodilator effect of histamine, diminishing the resistance to the flow in organs perfused by the natural circulation.

In what way did the conditions of natural differ from those of artificial perfusion? An obvious possibility was the existence of some nervous mechanism, which did not survive under the artificial conditions. I need not trouble you with the details of the investigations, by Laidlaw and myself, in which such possible nervous mechanisms, in the spinal cord, in the sympathetic ganglia, in the peripheral nerve-endings were, one by one, eliminated. I need only refer to the last stage of this elimination, which occurred in a recent renewal of the attack on this problem, in which I had the great privilege of coöperation with Professor Richards of Philadelphia. Richards and I found that, when all the nerves to a limb, or to a loop of the bowel, had been cut and allowed to degenerate completely, the dilating effect of histamine on the vessels, thus completely denervated, was not abolished, but, on the contrary, was habitually much intensified.

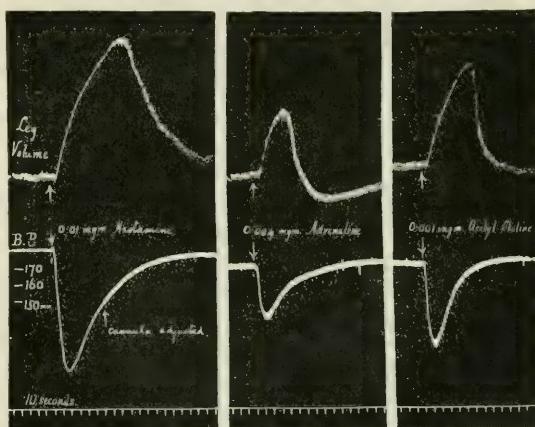


FIG. 1.—Volume of leg completely denervated by degeneration; blood-pressure. Intravenous injections as indicated. (Dale and Richards, Journ. of Physiol., LII, p. 120, Fig. 4.)

On the other hand, if such a denervated limb was artificially perfused with blood, the addition of histamine to the blood caused vasoconstriction of at least normal intensity. So that both the vasoconstrictor effect on the artificially perfused organ and the vasodilator effect on the naturally perfused organ were purely peripheral effects, independent of the integrity of the nerve supply. The paradox was more complete, more sharply defined than ever. We had no clue here to the missing factor in the artificial perfusion. What we believe to be the correct clue to the meaning of this paradox was first obtained from experiments which Laidlaw and I had already made on the effects of comparatively large, seriously poisonous doses of histamine. I shall have more to say concerning these later, but may mention now that they seemed, in large measure, to be due to a poisoning of the capillary endothelium. The suggestion that the evanescent, vasodilator action of small doses was also an action on the capillaries, that it represented not a relaxation of arterial tone,

but of an intrinsic tone of the capillary walls, began to take form in our minds. I believe Laidlaw first had the insight, or the hardihood, to give it expression. To consider it was to run counter to the accepted physiological teaching; but the paradox still awaited explanation, and we seemed to have exhausted other possibilities.

Richards and I attempted to put it to the test in two ways. In the first place, we endeavored to determine the conditions in the living animal which favored or accentuated the vaso-dilator effect of small doses of histamine. We studied the condition of the circulation in the hind limb of the cat, at different intervals after section of all the nerves, and we found what we regarded as evidence of independent variation of the

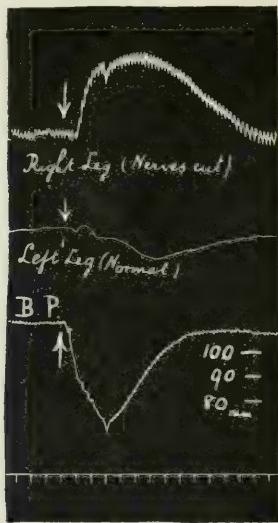


FIG. 2 (I).—Effect of 0.01 mgm. histamine. Volumes of leg with nerves freshly cut and of normal leg; blood-pressure. (Dale and Richards, *Journ. of Physiol.*, LII, p. 125, Fig. 7.)

tone of the arteries and the capillaries. There was one condition, in particular, appearing very soon after the nerves had been divided, which we could only interpret as due to dilatation of the arterioles and constriction of the capillaries. The volume-pulse of the limb, as registered by a plethysmograph, was greatly exaggerated, showing that the arteries were widely dilated; the skin in an unpigmented animal, best seen on the hairless pads of the foot, was pale, showing that the capillaries were constricted; and this combination of arterial relaxation and capillary tone produced a rapid circulation through the skin, so that the surface was warm. In the normal limb, on the other hand, especially in cold weather, the converse condition was observed; the volume-pulse was small, and the pads of the feet were red, but cold to the touch, which we regarded as indicating that a small stream of blood,

through constricted arterioles, was spread out to circulate slowly through a relaxed network of capillaries. When this contrast of warm pallor and cold congestion was well marked between the two limbs, there was always a pronounced contrast between the dilating action of histamine on the two. The pale and warm denervated limb, in which the capillary tone was good, always showed a well-marked expansion; the normal limb, with cold, red pads, showed a relatively very small expansion, or even an actual shrinkage with the fall of blood-pressure caused by histamine. In other words, it appeared to us that, irrespective of the condition of the arteries if the capillary tone was high, giving scope for capillary relaxation, the dilator effect of histamine was accentuated; but that, if the capillaries were already relaxed so that little further effect in that direction was possible, the dilator effect of histamine was weak or absent. It would



FIG. 2 (II).—Right sciatic and anterior crural nerves cut 5 days previously. Left leg normal. Effect of 0.01 mgm. histamine. (Dale and Richards, *Jour. of Physiol.*, LII, p. 132, Fig. 12.)

take too long to describe the corroborative evidence obtained by studying the effects on vessels subjected to temporary anaemia and cold. I can only say that it all seemed to point in the same direction, namely, to the conclusion that the vasodilator effect of histamine was an effect on the capillaries and not on the arteries. Then, in the second place, we made experiments on the conditions which would enable histamine to produce this vasodilator effect even in the perfused organ in which it had never hitherto been observed. We found the condition in a combination of two factors. (1) The supply to the tissues of abundant oxygen must be ensured by the presence of red corpuscles in the perfusion fluid; and (2) a small proportion of epinephrine must also be present. Neither alone was effective. The organ might be well oxygenated by using a suspension of red corpuscles or hirudinised blood; or epinephrine might be added to gum-saline solution so as to produce a high arterial resistance to perfusion; but histamine still increased the resistance to perfusion, retarded the venous outflow and caused shrinkage of the organ. Only if both

red corpuscles and epinephrine were added, and then always, did histamine produce in the perfused organ its normal effect, as produced by small doses in the living body—weakening of resistance, accelerated venous outflow and expansion of the organ-volume (Figs. 3, 4, 5 and 6). Note that in Fig. 3, when epinephrine alone is added, and in Fig. 5, when blood without epinephrine is used, histamine causes only vasoconstriction. Only in Figs. 4<sup>b</sup> and 6, when both red cells and

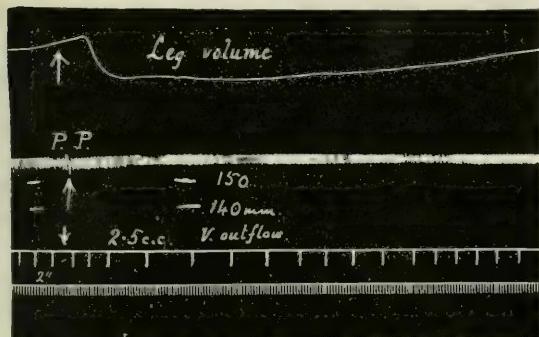


FIG. 3.—Perfusion of leg with gum-Ringer and adrenaline (1 in 2½ millions). Effect of 0.03 mgm. histamine. (Dale and Richards, Journ. of Physiol., LII, p. 150, Fig. 16.)

epinephrine are present, is the vasodilation effect to be seen. In these and other tracings acetylcholine is used, by way of contrast, as a typical *arterial* dilator, producing its vasodilator action under all conditions. This seemed to us again to point to the production of the vasodilator effect of histamine

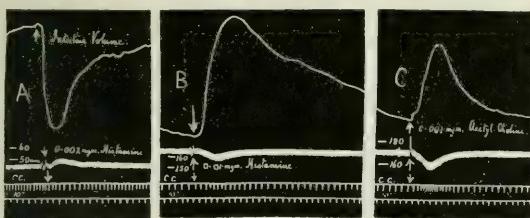


FIG. 4.—Perfusion of intestinal loop with hirudinised blood. Oncometer, perfusion pressure, and venous outflow. A before, B and C after addition of 1 part of adrenaline to 1 million of perfusing blood. (Dale and Richards, Journ. of Physiol., LII, p. 150, Fig. 17.)

by an action on vessels far more sensitive to an adequate oxygen supply than the arterioles. With arterial dilators, such as acetylcholine or the nitrites, there is no difficulty in demonstrating the vasodilator effect in an organ perfused with simple saline solution. The relation between the increase of organ-volume produced by histamine and its effects on the resistance and venous outflow seemed also to indicate its action on vessels more peripheral than those affected by an arterial dilator. It will be seen in Fig. 4 that that increase of

organ-volume produced by histamine is very large in relation to the acceleration of venous outflow. Finally we were able to put this idea to the test of an anatomical separation. We perfused the arteries in a triangular segment of mesentery, cut-

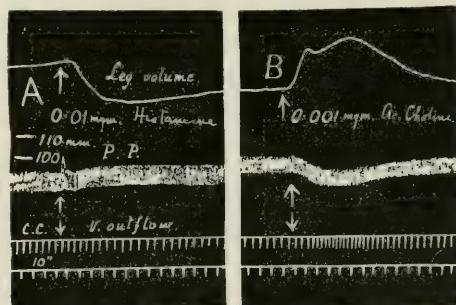


FIG. 5.—Completely denervated leg perfused with hirudinised blood (no adrenaline added). (Dale and Richards, Journ. of Physiol., LII, p. 151, Fig. 18.)

ting away the corresponding loop of intestine as close as possible to its mesenteric attachment and measuring the outflow from the open ends of the fine arterial branches thus cut across. Even when blood and epinephrine were perfused, histamine invariably caused further constriction, shown by retarded

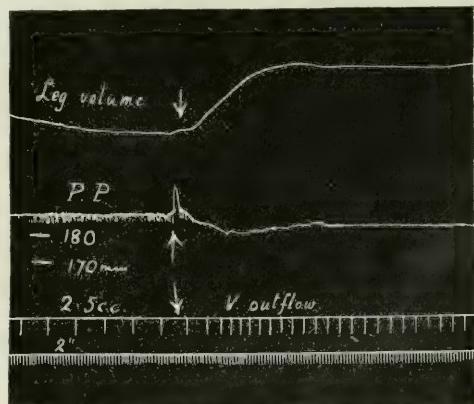


FIG. 6.—Perfusion of normal leg with hirudinised blood to which 1 part of adrenaline in 10 millions has been added. Effect of 0.1 mgm. histamine. (Dale and Richards, Journ. of Physiol., LII, p. 151, Fig. 19.)

outflow, while acetylcholine regularly caused relaxation (Fig. 7). Yet, under these same conditions the flow through the loop of bowel, containing the capillary distribution of these arterioles, had always been accelerated and its volume increased, by similar doses of histamine. We arrived then at a conception of the action of histamine on the blood vessels which involved a dual mechanism; an increase of the tone of the arterial plain muscle, and a relaxation of the tone of the

capillaries. Either effect might be predominant according to the conditions of the test. When the natural tone of the capillaries was good, the dilator effect on the capillaries was the conspicuous and effective factor, especially when the dose was small; for the sensitiveness of the capillaries to this action is extraordinarily high. As little as the 100 millionth part of a milligram has been observed to give a definite effect. On the other hand, if the capillaries were already relaxed, the effect on the arteries would predominate, and we should obtain a purely vasoconstrictor effect, as in the ordinary perfusion experiment, if either red corpuscles or epinephrine were absent.

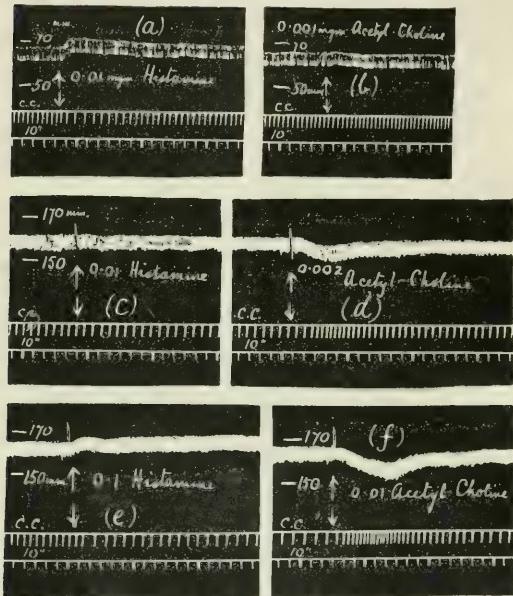


FIG. 7.—Perfusion of branches of superior mesenteric artery with hirudinised blood. (a) and (b) before, (c), (d), (e) and (f) after adding 1 part of adrenaline to 1 million of blood. Perfusion pressure and outflow from cut arterioles. (Dale and Richards, *Journ. of Physiol.*, LII, p. 157, Fig. 20.)

I hope I have succeeded in making clear the kind of evidence we obtained. It is difficult, with the necessary brevity, to give an impression of the effect of the different threads of argument converging to one conclusion. Yet the point is one on which I should like to carry conviction, for so much springs directly from it in the way of suggestion as to the physiological control of the circulation. The idea of an independent contractility of the capillaries is no new one. Since Stricker first credited them with this function in 1865, there have been numerous observations confirming the power of these vessels to vary their lumen from complete occlusion to wide patency, independently of the arterial pressure. Some, like Stricker himself, have attributed these changes to a varying turgescence of the capillary wall rather than to active con-

traction. Others, such as Rouget, Mayer and Steinach and Kahn, have described the capillaries as possessing a delicate coat of actively contractile cells, surrounding the endothelial wall, and comparable in function to the plain muscle coat of the arterioles. Roy and Graham Brown, while not committing themselves as to the exact nature of the process, were convinced that the contractility of the capillaries was not an occasional, abnormal function, but was always in action, so that these vessels had a tone of their own, capable of intensification or relaxation. While the existence of such a function was generally admitted, however, it was not until recently credited with more than a local and exceptional influence on the circulation. Langley thought that the shifting incidence of the state of contraction of capillaries might ensure that each section of a tissue received a supply of blood, under conditions of pressure too low to maintain a simultaneous circulation through the whole. Cotton, Slade and Lewis attributed some of the phenomena of dermographia, and the local pallor caused by epinephrine in a limb in which the circulation has been stopped, to action on capillary tone. But I think it may fairly be stated that, in the prevalent conception of the manner in which the circulation is maintained, of the nature of the peripheral resistance upholding the general arterial pressure and changing the distribution of the blood-flow in accordance with the needs of the tissues, the independent tone of the capillaries has played no part of any significance. It is believed that the effective resistance to blood-flow is in the arterioles, and that when the blood leaves these for the capillaries, it enters a region where the resistance is relatively trivial. Now if calculations be based on the sectional areas of the whole available capillary network, such a conclusion is inevitable, for the path then available for the blood is so wide, the rate of its flow correspondingly so slow, that the frictional resistance must be negligible as compared with that in the arterioles. A study of the rates of flow in a tissue such as the web of a frog's foot leads to a similar conclusion. On the other hand, if our results with histamine have been rightly interpreted, they indicate that, in the body as a whole, the capillaries in their normal state of tonus, contribute an effective part of the resistance to the blood-flow, so that a simultaneous weakening of the capillary tone over a large area may cause a fall of arterial pressure, by diminution of the peripheral resistance, very similar to that caused by arterial relaxation. This is a conclusion which those who have long been engaged in investigating and teaching the physiology of the circulation find very difficult to accept. On the ordinary conception of the capillary network, as depending for its state of fullness or depletion entirely on the tone of the arteries and the pressure in the veins, it would clearly be impossible. Indeed, I think, and shall presently show reason for believing, that when all the capillary channels are open and simultaneously available for the passage of blood, the capacity of the capillary network is such that a large part of the blood pours into it and stagnates as in a morass. Our view of the capillaries, under normal conditions, as opposing an effective resistance to the blood flow, necessarily entails the belief that

only a very small proportion of the available capillary paths, in the tissues as a whole, are at any one moment normally serving as a channel for the transmission of blood, the rest being closed by intrinsic tonus.

We should suppose that the incidence of this occlusion is constantly shifting, some paths opening as others close, but the average total path remaining fairly constant in the resting tissue, and remaining so small as to contribute effectively to the peripheral resistance. Under the influence of a small dose of histamine or of other substances acting in a similar manner, the channels already open would become wider, possibly to some extent channels completely closed would open, the resistance to blood flow would be diminished, and an effect on the arterial pressure very similar to that of an arterial dilatation would be produced.

We had already reached this conception by indirect argument from this action of histamine, when a paper appeared by Krogh, who had devised new and beautiful methods for directly observing the state of the capillaries, not merely in transparent membranes, as previous observers had done, but in the really effective tissues, the functional master tissues, such as the skeletal muscle, of which the large mass of the body is formed. Krogh was able to show that in the resting muscle of the frog or the mammal, the portion of the available capillary network actually in use is surprisingly small. On the other hand, in the active muscle a great number of additional channels were opened up and the paths became not only more numerous, but wider; so that, in one determination, the volume of blood in the active muscles of a guinea-pig was 275 times as great as in the muscle at rest, while the maximum blood content of the muscle, with all the capillary channels dilated, was no less than 750 times the minimum. Krogh, who investigated this mechanism from the point of view of the oxygen supply to the tissues, showed that only by such active variation in the lumina of the capillaries could the blood supply be adapted to the fluctuating needs of the tissue for oxygen.

From an entirely different point of view, therefore, Krogh reached a conception of the capillary circulation which fundamentally accorded with ours. It seems to me clear that, apart from the coarse adjustment of the blood supply to whole organs or areas of tissue, effected by the variations in arterial tone under the influence of the nerves or of epinephrine, we have to take account also of a fine adjustment of the blood supply to the varying needs of separate small areas of tissue, or even of individual cells, carried out by the changing tone of the capillaries. The question arises as to the mechanism by which this fine adjustment is controlled. Steinach and Kahn described a contraction of the capillaries in the frog's nictitating membrane when the sympathetic chain was stimulated, and Krogh has recently described a spread of capillary dilatation from a punctiform stimulus, apparently due to an axon reflex through the branched termination of sensory fibres. On the other hand, the body supplies abundant examples of a joint nervous and chemical control; and, if a momentary lapse into teleology be permissible, it may be

pointed out that an adjustment of the capillary flow to the local needs of the tissue would be most appropriately effected by the local action of the metabolic products of activity. Such a conception of the capillary dilatation which follows a temporary anemia was put forward by Roy and Graham Brown, who suggested that possibly even the effect of local irritation might have a similar origin. Barcroft has attributed the vasodilatation accompanying activity in the salivary gland to the action of metabolic products of the activity of the secreting cells. He was speaking of an arterial dilatation, which is the only factor in the increased blood supply that has hitherto received adequate recognition. I find difficulty in supposing that metabolic products, which enter the blood only after it has passed from the arteries, could reach the arterial muscle in sufficient concentration to produce this effect. There is no such difficulty in the conception of an action of this nature, by metabolic products, on the tone of capillaries, with their intimate relation to the active cells of the organ. If it could be supposed that substances, having the type of action that we have considered in the case of histamine, are formed in the tissues, and that their production is accelerated by functional activity, by any influence which renders the existing oxygen supply inadequate for the metabolic need, we should have a mechanism by which not only each organ, but each small part, or even each individual cell, could constantly effect a nice adjustment of the blood-flow to its need for oxygen, and for the removal of harmful waste by the cleansing stream of the circulation. At present such a conception is almost entirely speculative. There is practically no evidence for the production of substances acting like histamine during functional activity of the tissues. It is true, and possibly significant, that substances of this type can be extracted from most of the tissues, even when taken straight from the living body; so that not only by *post-mortem* change, but, at the latest, in the very act of death, such substances are liberated from the cells. To suppose that they are formed as the result of injury not involving death of the cells, or during normal functional activity, may seem a short step, but it is one of such importance that it cannot be safely taken without the support of direct experimental evidence. All that is definitely known of functional activity, such as muscular contraction or glandular secretion, is that it is attended by an increased consumption of oxygen and an increased production of carbon dioxide. Various observers have shown that slight increase of acidity, such as an addition of carbon dioxide to the blood, is attended by vascular relaxation, though whether of arterial or capillary tone has not yet been made clear. On the other hand, we have as yet no real experimental warrant for connecting increased tissue activity with immediate increase of protein breakdown, such as the production of histamine-like substances would seem to entail. It *may* take place, but its occurrence would be difficult to demonstrate, for the quantities needed to cause pronounced capillary dilatation would be so minute as probably to escape detection by the chemical methods available.

I must pass now from the consideration of the evanescent effect of very small doses of histamine to that of the more lasting effects of relatively much larger, though still absolutely small, doses of this powerful substance. We pass, in other words, from the physiological to the pathological signifi-

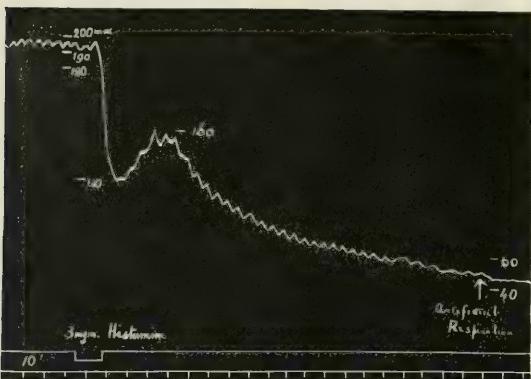


FIG. 8.—Cat. 2.350 kilo. (Dale and Laidlaw, *Journ. of Physiol.*, LII, p. 358, Fig. 1.)

cance of this type of action. From the conception of the dual action which I have already put before you, we might predict the results on the circulation of larger doses of histamine, producing the same type of action in a more intense and persistent form. We should expect, in the first place, that the stimulant effects on arterial plain muscle would come more

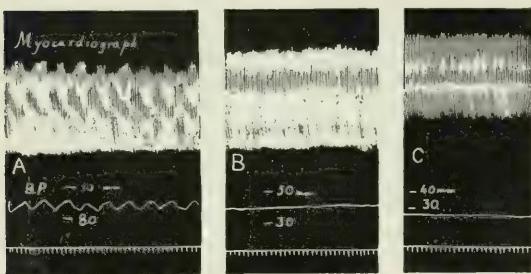


FIG. 9.—Cat. 2.6 kilo. A normal, B 6 minutes, C 18 minutes after injection of 5 mgm. of histamine. (Dale and Laidlaw, *Journ. of Physiol.*, p. 363, Fig. 9.)

into prominence, and, in the second place, that the general and long persistent dilatation of all the capillaries would lead to an accumulation of a large part of the blood in the peripheral reservoir thus opened for its reception. The arterial constriction would make this process slower, but, by more effectively cutting off the driving effect of the heart from the blood stagnating in the lax capillaries, would render it eventually more complete. This anticipation is exactly fulfilled. There is no immediate vasodilator fall such as follows the injection of a minute dose. On the contrary, in the cat

under ether there are preliminary phases of the effect which we were able to associate with constriction, first of the pulmonary and then of the systemic arteries. Then followed the main effect of a relatively slow fall of pressure, with a disproportionately rapid decline in the output from the heart (Fig. 8).

This decline of the output from the ventricles is not the result of weakening of the muscular contractions of the heart. These, indeed, are, surprisingly, as powerful as before the drug is given (Fig. 9). Inspection of the heart and great vessels reveals the cause of the condition; the heart and the arteries are almost empty and the great veins are only partly filled. Transparent tissues show a dusky flush of capillary congestion and a network of venules filled with dark blood. The circulation is failing, because the blood is not returning in sufficient volume to the heart to fill its chambers during diastole to more than a small fraction of their capacity. In some way the volume of blood in effective currency has been greatly reduced. One factor in this reduction becomes obvious when the corpuscular content of the blood is examined. In five minutes or so, after administration of 1 or 2 milligrams of histamine per kilogram, the proportion of red corpuscles and the corresponding haemoglobin value of the arterial blood are raised to a striking degree, often up to 50 per cent or more above the initial values. This is due to actual leakage of plasma from the vessels into the tissues, and a simple calculation shows that half or more of the original plasma may thus have been lost to the circulation in a few minutes. This, in itself, entails a material diminution of the absolute volume of fluid in the vessels. It is not enough, however, to account for the extreme deficiency of blood in circulation. Moreover, if the dose is slowly infused instead of being rapidly injected, an almost equally severe collapse of the circulation from defect of blood in currency, is produced with relatively small loss of plasma as indicated by the corpuscular content. Direct determination by the "vital red" method shows that the same decrease in the volume of effectively circulating blood has, nevertheless, occurred.

Laidlaw and I arrived at the conclusion that the real cause of the oligæmia was a general and simultaneous loss of their normal tone by all the capillaries in the body, so that the blood percolated into the lax network of channels as into a sponge. There was doubt at the time as to the possibility of the capillaries furnishing accommodation for so large a fraction of the blood as to bring about this peripheral stagnation and deplete so seriously the heart and great vessels. Any need for hesitation on this ground, however, has been sufficiently removed by Krogh's determinations, showing that in skeletal muscle at least, the capillaries when fully relaxed can accommodate 750 times the volume which they contain in the resting organ. If we can imagine any such multiplication of the capillary capacity as taking place throughout the body, I think there is no need to look further for the cause of the "oligæmia."

In interpreting these effects, on the circulation of the anæsthetized cat, as due to general loss of the normal tone of the

capillaries, associated with a greater or less development of an abnormal permeability of their walls to the blood plasma, we were not concerned with a mere pharmacological curiosity. No one with even a slight knowledge of the literature dealing with the experimental production of traumatic shock, embodying the observations largely made by your countrymen, could fail to be struck by the similarity of the condition which we were studying with that described as constituting circulatory shock, especially by Yandell Henderson, Mann and others. It was impossible to miss the suggestion that, in at least some of the conditions described as shock and especially in those involving massive injury to the soft tissues, a toxæmic factor might play a prominent part. One of the difficulties in the past had been to bring the experimental work on shock into proper relation with clinical observation, but the experience of surgeons in the late war provided opportunities for comparison in tragic abundance. There was a condition which a group of our military surgeons, with whom at the time was serving Professor Cannon of Harvard, came to recognize as "secondary shock"—a condition slowly developing some hours after extensive injury. We whose work kept us in England, formed a small Shock Committee, and by constant communication with the workers in France we came to realize with increasing clearness that the central feature of the secondary shock was the oligæmia which Henderson and Mann had recognized in their experimental work, and which we had found to be reproduced so faithfully in the effects of larger doses of histamine. The blood was concentrated, the corpuscular content of the capillary blood being notably greater than that of the venous blood. The effective volume of the blood in circulation was greatly reduced; Dr. Keith was able eventually to demonstrate this directly by the use of his "vital red" method. The condition was, with rare exceptions, complicated by haemorrhage; but, making full allowance for this and for loss of plasma into the tissues, the workers in France were convinced, as we had been, that there was a further loss by peripheral stagnation of blood. Professor Cannon's analysis of the condition, as he studied it in a British Casualty Clearing Station, showed a remarkable concordance with our description of the effects of histamine. Meanwhile, experiments carried out on behalf of your American Shock Committee by Professor Erlanger and his colleagues, with which we were kept in close touch by the kindness of Professor Howell, were leading them to a very similar conception.

It is, perhaps, hardly necessary for me to say that the members of our Shock Committee were making no claim or any attempt to interpret on these lines all the conditions, which have been classed as shock, or even as traumatic or surgical shock. We were simply impressed by the stray suggestion of a toxæmic factor as of central importance in the condition which the war surgeons called "secondary shock." Evidence of a more direct nature was not long wanting. Cannon and Bayliss in England produced the shocklike condition in anaesthetized animals by massive trauma of the muscles of a limb, and showed that severance of all nervous connection did not

affect the onset of the shock, while occlusion of the blood vessels prevented it. Quénau and Delbet in France had independently reached a similar view as to the importance in the genesis of shock of the absorption of autolytic products from injured tissues. They, as also McNee and Cannon, demonstrated the protective effect of occluding the blood vessels of the injured limb by pressure and had occasion to record the subsequent onset of shock when the blood was readmitted to the injured tissue. All this evidence emphasizes the probability that a central factor in the secondary wound-shock was the absorption from injured autolyzing tissues, and especially from injured muscle, of substances producing the same depressant effect on capillary tone, the same morbid permeability of the capillary walls, as that which we have been considering in the action of histamine. The analogy is made closer by the discovery that haemorrhage, as well as anaesthesia with ether or chloroform, enormously weaken the resistance to histamine, with which the healthy, unanaesthetized animal can deal in relatively very large doses.

It seems likely, therefore, that more than an accidental and superficial resemblance was involved in the similarity, recognized as long ago as the 1870's, between certain states of traumatic shock and the collapse resulting from a rapidly generalized infection. We arrive at the conception of a group of toxæmias, some of bacterial, some of traumatic origin, due to toxic substances having that same general action on the capillary circulation which we have been considering in the case of histamine. Whatever further chemical investigation may reveal as to the nature of such substances and their relation to histamine, I think there can be little doubt that this conception of the capillaries as an actively contractile part of the vascular system, having an intrinsic tone which can be modified either by nervous or chemical influences, is destined in the future to play a part of increasing importance in conceptions of the mechanism by which the blood supply to the tissues is regulated under normal physiological conditions and of the disturbances by which it is rendered pathologically inadequate.

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## A STUDY OF THE CARDIOVASCULAR REACTION TO EPINEPHRIN EPINEPHRIN SENSITIVENESS IN PATIENTS WITH HYPERTENSION

By PAUL W. CLOUGH

(From the Medical Clinic of The Johns Hopkins Hospital)

The possibility of utilizing as a diagnostic procedure the response of a patient to a subcutaneous injection of epinephrin was first brought to general notice by Eppinger and Hess.<sup>1</sup> They showed that in a number of cases, patients with Graves' disease responded to the injection of 0.001 g. of epinephrin with a marked rise in systolic pressure, tachycardia, mydriasis, glycosuria, and often with tremor, palpitation, and marked subjective nervous disturbances. Normal individuals, on the other hand, showed little or no response to this dose. Their claims that epinephrin sensitiveness is to be regarded as a fairly exact index of the tone of the sympathetic nervous system have not been entirely substantiated by subsequent observers, such as Barker and Sladen,<sup>2</sup> and Lehmann.<sup>3</sup> These later writers found, however, that in certain individuals, particularly in cases of thyroid intoxication, a state of marked epinephrin sensitiveness does exist.

More recently Goetsch<sup>4</sup> has advocated the use of the test as a diagnostic procedure in cases of thyroid intoxication, particularly in thyroid adenoma. He reported that after the subcutaneous injection of 0.5 c. c. of a 1-1000 dilution of epinephrin, a positive reaction was obtained with great uniformity in such patients, while in his experience it did not occur in individuals in whom thyroid intoxication could be excluded. He regarded a reaction as positive if a majority of the following symptoms developed: a rise of over 10 points in systolic blood pressure and in pulse rate, tremor, palpitation, throbbing of the peripheral vessels, flushing or pallor, asthenia, nervousness, anxiety, or an aggravation of previous subjective symptoms. His claims as to the frequency of positive reactions in thyroid intoxication seem on the whole to be receiving general confirmation, and the test is being used by some clinicians as a routine diagnostic procedure.

Peabody and his associates<sup>5</sup> employed the test in a study of soldiers with "irritable heart," and obtained positive reactions in 60 per cent of the cases. As these men did not show an increase in basal metabolism, as tested by Benedict's method, or definite clinical signs of thyroid disturbance, he did not regard the positive reactions as indicating increased thyroid activity.

Because of the increasing use of this test as a diagnostic procedure, it seemed desirable to put on record the observations included in this paper. The work was undertaken in order to study in detail the cardiovascular response to the drug, and to determine the frequency and degree of epinephrin sensitiveness in normal individuals and in a varied group of patients. Few cases of outspoken thyroid disturbance were included, but special attention was directed to patients with hypertension.

The patients were kept in bed for an hour or more before the test, and the blood pressure and pulse rate were recorded at frequent intervals until a constant level was established. A subcutaneous injection of 1 c. c. of a 1-1000 "adrenalin" solution\* was then given, care being taken that the needle did not enter a vein. In some cases the dose was reduced to 0.5 c. c., 0.66 c. c., or 0.75 c. c. Observations of the systolic and diastolic blood pressure were taken at intervals of one minute during the first 5 minutes after the injection, and then at intervals of two or three minutes for 20 or 30 minutes, or until the reaction was definitely subsiding. Further readings were then taken at 5-minute intervals until the original level was reached. Care was taken to avoid unnecessary excitement or movement on the part of the patient.

The blood pressure was determined with a Tycos instrument by the auscultatory method. The diastolic pressure was read at the point at which there was an abrupt diminution in the intensity of the sound at the end of the third phase. The duration of the fourth phase was often prolonged after epinephrin injections, and the point of complete disappearance of the sound was usually 10 to 20 mm. lower. While attention was chiefly directed to the cardiovascular reaction, the occurrence of glycosuria, mydriasis, palpitation, tremor, and any form of subjective discomfort was also noted.

The slight pain and excitement associated with the injection often caused a rise of 10 mm. in the systolic blood pressure which usually subsided after 1 or 2 minutes. As a rule, the blood pressure showed little change during the first 5 minutes following the injection. There was then a fairly rapid rise in systolic pressure to a maximum, reached after from 10 to 20 minutes, and often associated with a simultaneous fall in diastolic pressure. There was then a more gradual fall in systolic pressure to the previous level or to a point somewhat below it, the latter being reached in from 45 to 90 minutes. The tachycardia and lowered diastolic pressure sometimes lasted considerably longer. In some cases in which absorption was presumably slower, the reaction consumed about double this time. In other cases the rise began after 2 minutes, and the maximum was reached after from 5 to 10 minutes. This must be explained by more rapid absorption.

After intravenous injection (Chart V) the maximum systolic pressure was reached within  $\frac{1}{2}$  to  $1\frac{1}{2}$  minutes, it fell rapidly after 2 or 3 minutes, and reached the previous level within 5 or 6 minutes.

For purposes of discussion the reactions observed have been divided arbitrarily into four groups, according to their

\* Parke, Davis & Co.

intensity. In the first group were placed those cases giving a negative or insignificant reaction. The rise in systolic pressure was less than 15 mm. The rise in pulse pressure was less than 20 mm. and did not exceed 50 per cent of the initial pulse pressure. There were no subjective symptoms. This type of response was obtained in 40 per cent of all cases tested, and in 30 per cent of 32 normal individuals.

In the second group reactions classed as moderate were observed. In these cases (Chart I) there was a rise in systolic pressure of from 15 to 30 mm. and this was usually asso-

after the pressure had fallen. As a rule, the subjective symptoms were slight. Glycosuria occasionally occurred. Moderate reactions occurred in 24 per cent of all cases tested, and in 50 per cent of 32 normal individuals.

In the third group of reactions, classed as marked (Chart II), there was a rise in systolic pressure of from 30 to 50 mm. In some of these cases there was also a fall in diastolic pressure, often very brief. In others the diastolic pressure rose with the systolic pressure, but this rise was much less than the rise in systolic pressure, and the increase in pulse pres-

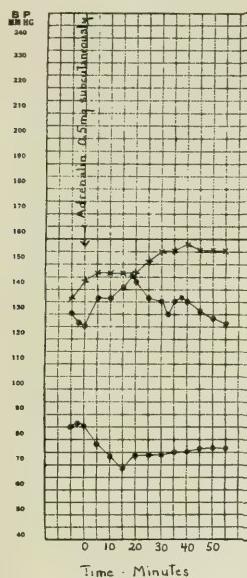


CHART I.—Moderate Reaction to Epinephrin.

Case No. 34723.—R. D., colored male, age 41.

Diagnosis: Myocardial insufficiency; chronic prostatitis.

There was a rise of 20 mm. in systolic pressure, associated with a fall of 18 mm. in diastolic pressure. The pulse pressure rose from 40 mm. to 75 mm., an increase of 87.5 per cent of the initial pulse pressure. The pulse rate increased 20 beats per minute, but the maximum rate was reached after the systolic pressure had fallen nearly to the initial level. There were no subjective symptoms.

ciated with a simultaneous fall in diastolic pressure of from 10 to 20 mm. There was therefore a marked rise in pulse pressure of from 25 to 40 mm. which amounted to from 50 per cent to 100 per cent of the initial pulse pressure. There was a striking change in the character of the sounds heard over the vessels; they became louder, very clear, and booming, so that it was easy to get sharp, accurate readings of both the systolic and diastolic pressures. The pulse rate usually rose 10 to 20 beats per minute. The tachycardia, as a rule, followed the rise in systolic pressure, often began only after the maximum pressure was reached, and reached its height

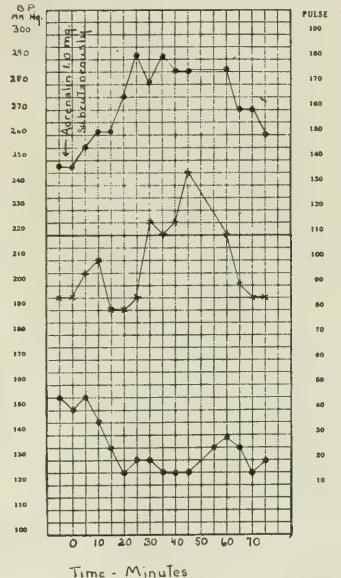


CHART II.—Marked Reaction to Epinephrin.

Case No. 33506.—E. N., colored male, age 58.

Diagnosis: Obesity, hypertension, myocardial insufficiency, chronic nephritis (?). No definite signs of hyperthyroidism.

On admission to the hospital the pulse was irregular in force and rhythm. Some beats were audible with a pressure of 310 mm. The patient was free from symptoms at the time the test was made.

The systolic pressure rose 45 mm., from 242 to 287 mm. The rise was more gradual than that shown in Chart III, the maximum being reached 30 minutes after the injection. The diastolic pressure fell 30 mm. The pulse pressure rose from 92 mm. to 167 mm., a rise of 75 mm., or 82 per cent of the initial pressure. The pulse rate rose from 80 to 130, but the maximum systolic pressure was reached before the rise began. The subjective discomfort was very marked. There was a rigor, sweating, polyuria, palpitation, extrasystoles, throbbing in the head, a "sick" feeling, mydriasis, and glycosuria of 5.5 g.

sure was always the striking feature. The increase in pulse pressure in this group was between 40 and 60 mm. or from 75 per cent to 200 per cent of its initial height. Pallor of the skin and mucous membranes was frequently observed. Such reactions were given by 23 per cent of all cases tested, and by 12.5 per cent of 32 normal individuals.

In the fourth group, giving very marked reactions (Chart III), the rise in systolic pressure was from 50 to 100 mm., while the pulse pressure increased about an equal amount, or between 75 per cent and 200 per cent of its initial height. Such reactions were obtained in 13 per cent of all cases tested, including 2 of 32 individuals regarded as physically normal.

In those cases showing a marked cardiovascular response, subjective symptoms were usually present. As a rule, these

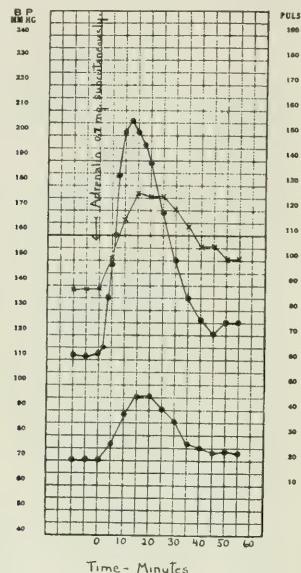


CHART III.—Very Marked Reaction to Epinephrin.

Case No. 34207.—H. C., colored male, age 68.

Diagnosis: Syphilis (Wassermann reaction), arteriosclerosis, hypertension, myocardial insufficiency. No signs of thyroid intoxication.

The blood pressure on admission was 150/100. At the time the test was carried out the symptoms of myocardial insufficiency were relieved, and the blood pressure was normal.

The systolic pressure rose 95 mm., reaching the maximum 12 minutes after the injection. The diastolic pressure rose 25 mm. The pulse pressure was nearly trebled, rising from 42 mm. to 112 mm. The pulse rate rose 40 beats per minute. Pulsus alternans developed during the reaction. There were nervousness and palpitation of moderate degree. No glycosuria.

patients complained of nervousness, palpitation, a sense of fluttering in the chest and throbbing in the head. Tremor was frequent, and in a few cases there was a violent chill. In the most severe reactions there was often precordial pain, anginoid in type, associated with great anxiety and marked subjective discomfort, difficult for the patient to describe. The palpitation, tremor, anxiety and discomfort sometimes occurred in patients giving only a moderate cardiovascular response, and the intensity of these symptoms was not in direct proportion to the circulatory changes. Glycosuria was often present, but it also did not parallel the blood pressure response. Hamman and Hirschman<sup>7</sup> have shown that the

rise in blood sugar also does not parallel the rise in systolic pressure.

In one patient, who was suffering from thyroid intoxication with marked nervous manifestations,\* a paradoxical reaction was observed. The blood pressure fell from 165/110 to 140/100 in the course of an hour. The pulse rate was unchanged, at 108 to 112. However, the sounds over the vessels became characteristically sharper and more thudding, and

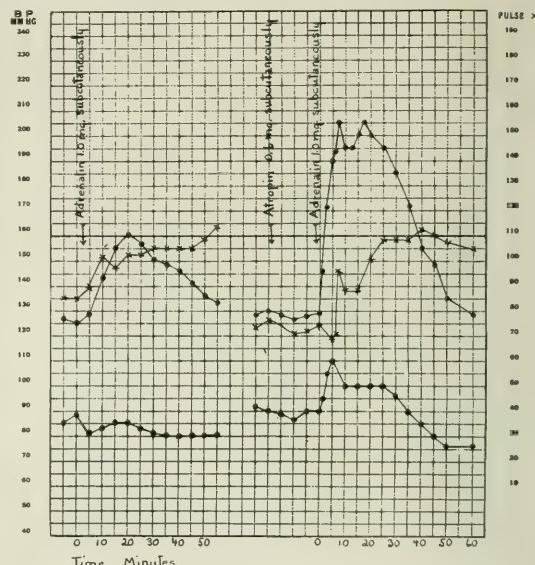


CHART IV.—An Exaggerated Reaction to Epinephrin, Following the Administration of Atropin.

Case No. 34031.—J. M., colored male, age 34.

Diagnosis: Acute rheumatic fever; syphilis (Wassermann reaction). No signs of thyroid intoxication.

Following the injection of 1 mg. of epinephrin there was a fairly marked reaction, with a rise of 33 mm. in systolic pressure, and of 37 mm. in pulse pressure. Two days later, when the same dose was administered 15 minutes after a subcutaneous injection of 0.0006 gm. of atropin, a greatly exaggerated reaction was obtained. The systolic pressure rose 78 mm., from 122 mm. to 200 mm. The pulse pressure rose from 38 mm. to 105 mm., treble its initial height. The pulse rate rose from 70 to 110 per minute, but here also the maximum systolic pressure was nearly reached before the tachycardia began. The patient felt "nervous," and extra-systolic arrhythmia appeared. There were no other symptoms, no mydriasis, and no glycosuria.

there developed tremor and palpitation. The skin near the site of injection became very markedly blanched, and absorption was evidently very slow. It seems probable that this reaction is comparable to the results observed in animals, where a fall in blood pressure may follow the intravenous injection of a minute dose of epinephrin, which is not sufficient to cause a rise in pressure.

In several other cases a transient fall of 10 to 15 mm. in systolic pressure occurred 2 to 5 minutes after the injection,

\* Seen through the courtesy of Dr. Emil Goetsch.

preceding a rise in pressure. This may be explained in a similar manner.

Atropin, administered hypodermically in doses of 0.6 to 0.8 mg. may cause a marked increase in the response to 1 mg. of epinephrin, given 10 to 15 minutes later, or it may cause a sharp epinephrin reaction in a patient who did not react to epinephrin alone. This is illustrated by the chart of J. M. (Chart IV.) Whereas 1 mg. of epinephrin caused a rise of 30 mm. in systolic pressure, a rise of 75 mm. occurred when the epinephrin injection was preceded by 0.6 mg. of atropin. Such an increased response is often associated with a rise in the pulse rate, but it cannot adequately be explained on that basis. As in this case the rise in blood pressure may precede the tachycardia, the maximum pressure may be reached or closely approximated before the rise in pulse rate begins, and the blood pressure is usually falling before the tachycardia reaches a maximum. Atropin seems to exaggerate the cardiovascular response to epinephrin without changing its character. Of 14 subjects tested, 8 showed an increased epinephrin response after atropin. It did not increase the tendency to glycosuria.

In bringing about this cardiovascular response, therefore, epinephrin must act in two ways; first, by causing a vasoconstriction of the small arteries, and secondly, by directly stimulating the heart, causing not only acceleration of the rate, but also augmentation of the force of the beat, and increase in the volume output. This direct stimulation of the heart seems to be the more important factor in the reaction. It seems impossible to find any other satisfactory explanation for the marked increase in pulse pressure, and particularly for the fall in diastolic pressure, so often associated with the increase in systolic pressure. Vasoconstriction alone could not do this. This view is supported by the visible precordial heaving, and by the sense of palpitation complained of during the reaction, which may be out of all proportion to the degree of rise in the systolic pressure.

In the more severe reactions vasoconstriction seems to play a more prominent rôle. Here the diastolic pressure also tends to rise, and there is often visible pallor of the skin and mucous membranes, while a sense of coldness of the skin is complained of by the patients. This is in accord with the well-known vasoconstricting action of the drug in animal experiments. The dose used in these clinical tests (0.015 to 0.02 mg. per kilo of body weight) is very small compared with the doses customarily employed in animal experiments, and exactly parallel results are not to be expected. Both the cardiac and the vascular responses are undoubtedly the result of stimulation of the sympathetic endings.

In all, tests were carried out on 95 subjects. Of these, 32 were either normal controls, or patients who were regarded as physically normal. Of these, 32 per cent gave negative reactions, 50 per cent moderate reactions, and 18 per cent marked reactions.

Individuals who were emaciated and cachectic, and who had a low blood pressure, especially if this was associated with diarrhoea or chronic organic disease, usually gave no response

(80 per cent of 15 cases). Marked reactions were obtained in 4 patients, in whom the malnutrition and hypotension were associated with asthenia, nervousness, tremor, mental depression with irritability, and digestive disturbances. It is possible that thyroid intoxication may have played a rôle in these cases.

One of these patients gave a marked general reaction with rigor, palpitation, extrasystoles, precordial pain and oppression, and glycosuria. On attempting to repeat the test a few days later, the patient objected strongly to the test, and became greatly excited, so that the injection was not given. Nevertheless, there was a rise in blood pressure to about the same height as that reached in the reaction, and glycosuria again occurred. Apparently there had been an outpouring of endogenous epinephrin under emotional excitement.

In diabetes mellitus, slight or moderate reactions were obtained in 5 of 6 cases. In 8 cases showing marked evidences of endocrine disturbance other than hyperthyroidism, moderate or negative reactions were obtained.

One patient with amyloid disease, secondary to chronic pulmonary tuberculosis, gave no response to a subcutaneous injection of 1 mg. of epinephrin. However, a sharp rise of 50 mm. in systolic pressure followed the intravenous injection of 1 c. c. of a 1:10,000 dilution. Although this is a marked reduction below the average in sensitiveness, it nevertheless demonstrates that the vessels were capable of contracting.

The most striking finding was the frequency of marked reactions in patients with hypertension. A systolic pressure of 155 or over was adopted as a criterion of hypertension. However, a few patients have been included in whom a high blood-pressure reading was obtained on the first examination, although the pressure had fallen approximately to normal at the time the test was performed. Of 22 cases tested,\* 15, or 68 per cent, gave marked reactions to 1 mg. of epinephrin, whereas such reactions were obtained in only 26 per cent of the 68 other cases tested, and in only 18 per cent of 32 normal individuals. This sensitiveness is shown more strikingly in the large percentage of very marked reactions observed, with a rise in systolic pressure of over 50 mm. Of the 22 cases of hypertension, 11, or 50 per cent, gave such reactions, while of 66 other cases (excluding exophthalmic goitre) only 2, or 3 per cent, so responded. Of the 15 cases of hypertension giving marked reactions, glycosuria was observed in 3 cases, mydriasis in 6, palpitation in 7, extrasystolic arrhythmia in 2, pulsus alternans in 1, and marked subjective discomfort or anxiety in 8. In several there was pallor of the skin and mucous membranes, and in 9 a rise in diastolic as well as in systolic pressure, indicating that vasoconstriction played a rôle in the reaction. Marked reactions were obtained, regardless of the degree, duration, or cause of the hypertension.

In none of these 15 cases were there any noteworthy "sym-pathicotonic" symptoms in the sense of Eppinger and Hess,

\* Five subjects giving slighter reactions to smaller doses of epinephrin have been omitted because it was considered inadvisable to repeat the test in these individuals with a full dose.

nor were there signs of thyroid intoxication, unless it were slight protrusion of the eye-balls, widened lid-slits, and a positive lid-lag. Only 2 of the 15 cases showed definite evidence of any endocrine disturbance. One of these showed a slight degree of hypothyroidism, and the other the same condition in a very pronounced degree.

What is the significance of this epinephrin sensitiveness in patients with hypertension? Can it be used in support of the view that hypertension is the result of a suprarenal overactivity, of an hyperadrenalinæmia? To interpret correctly a pathological response to epinephrin we must have a thorough understanding of its pharmacological and physiological action. But, while the pharmacological action of epinephrin causing a stimulation of all the sympathetic nerve endings in the body is well established, the exact rôle which this substance plays in the normal physiological activities of the body is still unsettled. It is known that epinephrin is constantly being formed in the suprarenal medulla, and that it is secreted into the blood of the suprarenal vein. The general asthenia, low blood pressure, and enfeeblement of the circulation which occur in Addison's disease, and in experimental animals as a late result of removal of both suprarenal glands, in conjunction with other facts, have led many to the assumption that epinephrin serves to keep the sympathetic system, and in particular the cardiovascular structures which it innervates, in a state of constant activity or tone.<sup>8</sup>

This view is based on the assumptions: (1) That epinephrin is constantly present in effective quantities in the circulation, and (2) that the normal physiological action of epinephrin, in the concentration in which it is actually present in the blood, is qualitatively the same as that manifested by the relatively enormous doses used in animal experiments. For neither of these assumptions is there any conclusive evidence. The amount of epinephrin constantly present under "normal" conditions in the circulating blood has never been accurately determined. The most trustworthy estimates are based on a determination in animals of the concentration of epinephrin in the blood in the suprarenal vein, and a comparison of the rate of flow of blood in the suprarenal vein with that in the aorta. Such estimates made by Hoskins and McClure<sup>9</sup> indicate that the concentration of epinephrin in arterial blood cannot be much over 1 in 200,000,000, an amount not detectable by any known methods. Their estimates are substantially confirmed by the findings of Stewart and Rogoff.<sup>10</sup> Since epinephrin is rapidly removed from the blood and destroyed in its passage through the tissues, there is no opportunity for any appreciable accumulation in the blood. It is practically absent from venous blood.

Furthermore, it has been shown by Cannon and Lyman<sup>7</sup> that epinephrin in high dilution (though more concentrated than that probably present in normal blood) causes a vascular dilatation with a fall in blood pressure. Hence if epinephrin in the circulating blood normally exerts any effect on the vascular tone, it would presumably cause a depression rather than a stimulation.

The observations recorded in this paper, however, suggest that the minimal quantity of epinephrin required effectively to stimulate the human cardiovascular system is much smaller than might be expected from animal experiments. The writer found that 1 c. c. of a 1 to 50,000 dilution, injected intravenously, frequently sufficed to cause a distinct reaction with a rise in systolic pressure of 20 to 40 mm. (Chart V). In a man weighing 65 kilos, this quantity, if diluted with the estimated total blood volume, would give a concentration of approximately 1 in 200,000,000. The maximum possible "normal" secretion of epinephrin in animals, as estimated by Hoskins and McClure, would therefore be about equivalent

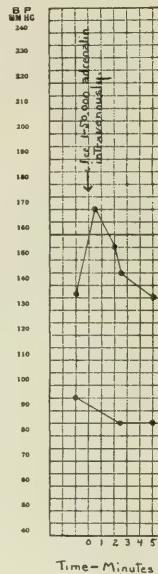


CHART V.—Moderate response to the intravenous injection of epinephrin.

Case No. 34901.—J. Q., white male, age 24.

Diagnosis: Acute nephritis; continued fever; tuberculosis of the spine. Slight renal insufficiency.

The dose was 1 c. c. of 1-50,000 dilution of epinephrin. There was a rise of 35 mm. in systolic pressure, reached about 30 seconds after the injection. The pressure fell practically to the initial level after 2½ minutes. The diastolic pressure was not accurately determined at the height of the reaction.

to this minimal stimulating dose in man. Several considerations, however, prevent one drawing any far-reaching conclusions from this parallelism. In the first place the epinephrin injected was not immediately diluted with the entire volume of blood, but reached the heart in a concentration considerably higher than 1 in 200,000,000. As pointed out above, the direct stimulation of the heart seems to be at least as important a factor as vasoconstriction in the milder reactions in man. Furthermore, if there be normally a continuous liberation of epinephrin into the blood, the effective stimulating dose is really the sum of that normally liberated into the

blood plus that injected. The additional quantity of epinephrin required to make effective a dose which is just subliminal may be a relatively small proportion of the total effective dose. Then again the normal rate of liberation in man may be different from that in animals.

More direct evidence that the maintenance of a normal blood pressure is independent of epinephrin liberation has been brought by Stewart and Rogoff.<sup>11</sup> These authors found that in cats, by removing one adrenal and cutting the nerves of the other, the normal liberation of epinephrin could be abolished or reduced to less than one per cent of the normal for many weeks, without impairing the health of the animals or affecting their blood pressure.

It seems well established, therefore, that epinephrin is not the direct means of maintaining blood pressure at the normal level.

It has been shown that the rate of liberation of epinephrin is under the control of the central nervous system, and evidence has been brought forward by Cannon and his associates<sup>12</sup> to show that in cats this secretion is subject to a marked temporary physiological increase under such emotion or exertion as is habitually encountered in the life of the animal. While the validity of Cannon's conclusions has been questioned, notably by Stewart and Rogoff<sup>10, 13</sup>, there is strong evidence that under natural conditions a temporary outpouring of epinephrin may occur which is sufficient to produce symptoms and to cause a rise in blood pressure. As pointed out above, the quantity which suffices to do this is relatively small and well within the presumable capacity of the glands to secrete. It is quite conceivable, therefore, that under pathological conditions the secretion of epinephrin might be abnormally increased. If such an increase in epinephrin liberation occurred and persisted, the resulting overstimulation of the sympathetic endings might readily cause distinct symptoms of disease. Such a condition of increased secretion, it has been claimed, would give rise to a state of increased sympathetic tone (*sympathicotonic*), assuming that the effect of a pathological increase of epinephrin in the circulation would be a simple exaggeration of its supposed physiological action. Hypertension might be one manifestation of such a "sympathicotonic" state. This assumption received some apparent support from the demonstration by Kretschmer<sup>14</sup> that in animals blood pressure can be maintained at a high level by the slow continuous infusion of a dilute solution of epinephrin.

As a matter of fact nothing definite is known as to the occurrence or the effects of a persistent increase of epinephrin in the circulation. Experimentally it has not been possible to produce a condition of hyperactivity of the suprarenals. Repeated injections of epinephrin do not give rise to a comparable condition, because of the very transient action of the drug. Continuous infusions can only be maintained for a few hours at most.

There is no direct evidence of an increase of epinephrin in the blood in human disease. Such an increase was reported by Schur and Wiesel<sup>15</sup> in chronic nephritis with hypertension, but their results were not confirmed by subsequent

observers. An increase was also reported in Graves' disease by Fraenkel,<sup>16</sup> by Kraus and Friedenthal,<sup>17</sup> by Bröking and Trendelenburg,<sup>18</sup> and by Adler.<sup>19</sup> All of these investigators used serum in their experiments and all except Adler applied it to test objects (frog's eye, rabbit's uterus, frog perfusion preparation) which respond to epinephrin by a contraction of smooth muscle. The validity of their results has been overthrown by O'Connor.<sup>20</sup> He showed that during the process of coagulation of the blood, substances entirely distinct from epinephrin appear, which cause a direct stimulation of smooth muscle, regardless of its innervation, and thus imitate the action of epinephrin. Citrated plasma did not manifest this activity. It is therefore necessary to use plasma and not serum in testing for epinephrin in the blood, or, if serum be used, to apply it also to test objects like strips of intestine<sup>21</sup> or coronary artery,<sup>22</sup> which respond to epinephrin by a relaxation and not by a contraction. Using the most sensitive method available, the frog perfusion test of Trendelenburg, O'Connor was able to detect epinephrin in plasma only from the blood of the suprarenal vein. He did not find any detectable epinephrin in the plasma from cases of Graves' disease.

These negative results are not absolutely conclusive, however, since these observers used venous blood in their investigations. A complete reinvestigation of this problem, using human plasma or serum obtained by arterial punctures would be very desirable, though it seems probable that the concentration of epinephrin even in arterial blood would be too small to be measurable by present methods.

The rate of liberation which would be required to maintain a hypertension is probably greater than the normal rate of secretion can be, and as pointed out by Hoskins and McClure,<sup>23</sup> would probably cause inhibition of intestinal peristalsis, glycosuria, and other disturbances of bodily function which are not present in hypertensives.

While Levy<sup>24</sup> found that in cats, with the thyroid intact, the administration of a single dose, or of several repeated doses of epinephrin, increased the response to a subsequent injection, Hoskins and Rowley<sup>25</sup> found that continuous infusions of epinephrin, regardless of whether or not they influenced the blood pressure, tended to diminish the response to an injection of an additional quantity of epinephrin, as well as to other forms of sympathetic stimulation.

The available evidence, therefore, does not support the conclusion that hypertension is due to, or associated with, a suprarenal hyperactivity, or a "hyperadrenalinæmia."

May this epinephrin sensitiveness in patients with hypertension be attributable to a state of hyperthyroidism, or thyroid intoxication? It was shown by Levy<sup>24</sup> that in cats any mode of stimulation of thyroid secretion increases the pressor effect of a subsequent injection of epinephrin. The association of epinephrin sensitiveness with unquestionable conditions of thyroid intoxication has been referred to. In some patients with hypertension there is a thyroid intoxication which is probably to be regarded as the cause of the hypertension. The latter symptom, however, occurs in a relatively small proportion of the cases of exophthalmic goitre or toxic adenoma,

and in the great majority of patients with hypertension there is no definite evidence of thyroid disturbance. It seems very doubtful if any such direct relationship between the two conditions exists.

It seems probable, therefore, that the increased sensitivity to epinephrin injections in hypertension may be only one manifestation of a condition of increased reactivity on the part of the cardiovascular system to stimuli of all kinds. These patients often show an unusually marked change in blood pressure in response to exercise, emotion, or excitement. This sensitiveness might depend on an abnormal state of the sympathetic system, or the nerve endings, without assuming an overactivity of either the chromaffin system or of the thyroid.\*

#### SUMMARY

There is a marked difference in the cardiovascular reaction of different individuals to a subcutaneous injection of 1 mg. of epinephrin.

The reactions observed has been classified arbitrarily, according to their intensity, as negative, moderate, marked and very marked. In a moderate reaction there was (1) a rise of from 15 to 30 mm. in systolic blood pressure, associated usually with (2) a fall of from 10 to 20 mm. in diastolic pressure. The striking feature of the reaction was (3) the increase in pulse pressure, which was often doubled. There was usually (4) a slight tachycardia. Other symptoms were usually slight.

In marked reactions the systolic pressure rose from 30 to 100 mm. There was usually a slight rise in diastolic pressure also, and a marked rise in pulse pressure. There was sometimes glycosuria, and very often tachycardia, palpitation, pallor, mydriasis, tremor, nervousness, and anxiety.

There must be two factors concerned in these reactions: (1) a direct stimulation of the heart, with increase in the force of the beat, and in the volume output, as well as in the rate; (2) constriction of the peripheral vessels. In the moderate reactions the first factor plays the chief rôle, whereas in the severe reactions vasoconstriction is also of importance.

Atropin frequently exaggerates the response to a subsequent injection of epinephrin.

Of 32 normal individuals 82 per cent gave a slight or moderate response.

Patients with hypertension often showed severe reactions to 1 mg. or less of epinephrin. Marked responses were obtained in 68 per cent of 22 cases, whereas they occurred in only 18 per cent of 32 normal individuals. This epinephrin sensitiveness occurred irrespective of the cause, the degree, or the duration of the hypertension. None of these patients showed evidences of significant endocrine disturbance.

It seems probable that this epinephrin sensitiveness in hypertension may be only one manifestation of a general abnormal reactivity of the cardiovascular system to stimuli of all kinds,

\* As the dose of epinephrin used in these tests was larger than that recommended by Goetsch, these findings, of course, do not invalidate his claim that sensitiveness to a subcutaneous injection of 0.5 mg. indicates a state of active thyroid intoxication.

and that it need not be attributed to a hyperactivity of either the chromaffin system or of the thyroid.

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## A CLINICAL STUDY OF THIRTY-NINE CASES OF COMBINED THORACIC AND ABDOMINAL WOUNDS

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In another paper we<sup>1</sup> have presented a study of 160 penetrating war wounds of the thorax and outlined, from a study of our series, the form of treatment which seemed to promise the best results. In that series were included fifteen cases in which we have either operative, X-ray, clinical, or autopsy proof that the diaphragm was perforated and some injury, although slight, to the abdominal viscera was sustained. The thoracic injury, however, far overshadowed the abdominal in severity, and because of this fact the cases were included in the penetrating thoracic wounds. In the present paper I shall study the combined thoracic and abdominal wounds, considering them, as I think they should be, as a special type of injury. For the sake of completeness in this study, I shall include the 15 cases above, and add to this number 24 cases not previously considered. Our series, then, consists of the following 39 cases:

(1) Twenty-one cases under my care at Evacuation Hospital No. 1. (2) Fifteen cases, operated upon by a group of surgeons at Evacuation Hospital No. 1 during September, 1918. The cases were seen and examined by me, then acting in the capacity of triage officer. After operation they were under my care. (3) Three cases treated at Base Hospital No. 18 at a time when it functioned as an evacuation hospital.

For convenience of study, these cases may be divided into three groups: a group of four patients moribund on admission, for whom no treatment excepting measures to combat shock was possible; a group of six patients not operated upon primarily but treated expectantly; and a group of twenty-nine patients subjected to immediate operation.

*Group 1.—Four Patients Admitted in a Moribund Condition.*—These were among the most seriously injured seen at an evacuation hospital. They were admitted in a condition of profound shock and with cough, hemoptysis, dyspnea, cyanosis, abdominal pain, and vomiting. On examination they presented open "sucking" chest wounds and signs of abdominal irritation. The chest wounds were immediately closed by strapping with adhesive, and the patients sent to the shock ward where the usual measures to combat shock were tried. In no case was there any response to shock treatment, and they died within a few hours after admission. Autopsy showed open chest wounds, lacerated wounds of the lower lobe of the lung, lacerated wounds of the diaphragm, and large lacerated wounds of the liver, stomach, or colon. In no case did autopsy indicate that there was hemorrhage

sufficient in itself to account for death; indeed, hemorrhage was rather insignificant. Death was due presumably to shock, the result of open pneumothorax and extensive wounds of important organs.

*Group 2.—Six Patients Not Primarily Operated Upon.*—In this group there were two bullet wounds and four shell wounds; five were penetrating wounds with retained missiles (of which four were shell fragments, one a bullet) and one a perforating wound with wound of entrance and exit; all were closed wounds. In character the wounds were all punctured wounds without extensive laceration of the soft parts and in only one instance with a moderately extensive rib fracture. In position the wounds were all upon the right side of the body. Five were pure thoracic wounds, the wounds of entrance located upon the lateral thoracic wall between the fifth and eighth ribs in four cases; upon the posterior thoracic wall at the level of the tenth rib in one case. One was a perforating wound, the wound of entrance upon the right back below the costal margin, the wound of exit at the level of the seventh rib just lateral to the right nipple line. The most common wound, therefore, was the shell wound which penetrated the lateral thoracic wall between the fifth and eighth ribs and coursed obliquely downward and inward. The foreign body in the five cases with retained missiles was lodged in the liver in four cases, in the thorax and against the spine in one case. In size, two shell fragments were over 1 cm. but less than 2 cm. in diameter; two were less than 1 cm. in diameter. In one case a machine-gun bullet had been retained.

Shock was profound in two cases, moderately severe in two cases, and practically absent in two cases. Under appropriate measures shock was recovered from in all the cases.

*Hemothorax* was massive and associated with marked cardiac displacement in two cases; of moderate grade (reaching the angle of the scapula) in four cases. Aspiration of 1000 c.c. of blood on three successive days for mediastinal compression symptoms was necessary in one case.

Symptoms and signs of abdominal irritation were present in three cases, absent in three cases. In two cases the symptoms and signs were upper abdominal pain and tenderness and rigidity chiefly of the right upper quadrant; in one case the abdomen was retracted and rigid, resembling the abdominal picture of an acute perforation of a hollow abdominal viscus. In none of the cases was there hiccup or vomiting.

*Clinical Course.*—Only one patient in the series pursued an uncomplicated course to recovery. The remaining five patients developed infectious complications. Three patients developed infected hemothorax, two of whom were treated by rib resection and drainage with subsequent sterilization of the cavities; one by repeated aspirations. All of the three recovered. One man with multiple serious wounds in addition to his thoracic injury, developed gas gangrene of the left leg for which a thigh amputation was done. He died with all the symptoms of gas intoxication. At autopsy, a clinically unsuspected abscess of the middle lobe of the lung was found about a bone fragment. The foreign

<sup>1</sup> Heuer, Pratt and Mason: A clinical study of 160 penetrating war wounds of the thorax. To be published in the *Annals of Surgery*, November, 1920.

body was embedded in the liver and perfect healing had taken place. One patient developed a lobar pneumonia involving the upper and lower lobe of the lung contralateral to the injury, from which he died. At autopsy perforating wounds of the right lower lobe of the lung, of the right lobe of the liver, and the upper pole of the right kidney were found. There was no reaction about these wounds. The infectious complications in all these cases, therefore, were entirely referable to the thoracic wounds, in no instance to the abdominal injuries.

*Treatment.*—The treatment in this group was the same as that for simple thoracic injuries. Rest in bed, morphin when necessary and aspiration for the treatment of hemothorax, were the measures employed until infectious complications appeared. Aspiration for the hemothorax was performed in four cases, not performed in two cases. Infected hemothorax was treated by rib resection and drainage in two cases, one of which was a gas bacillus infection. A third patient, in whom the streptococcus viridans was the infecting organism, was treated by repeated aspiration and recovered without the development of a frank empyema.

*Results.*—One patient recovered without complications; five patients developed infectious complications, of which three recovered and two died. Mortality, 33½ per cent.

**GROUP 3.—Twenty-Nine Patients Subjected to Immediate Operation.**—In this group there were 28 shell wounds, one bullet wound; 27 were penetrating wounds with retained missiles, two were perforating wounds. Twenty-seven were thoracic wounds—of the right thorax in 17 instances, of the left in 10 instances; two were abdominal wounds which had penetrated the thorax. Of the thoracic wounds, 10 were open and sucking, 17 were closed.

The position of these wounds will be indicated in the following paragraphs. In character, the wounds varied from large lacerated open wounds with extensive rib fractures, to small closed wounds without much tissue destruction. Ten of the thoracic wounds, as above noted, were large open sucking wounds, 17 were small punctured closed wounds. Extensive rib fractures (from one to five ribs) occurred in thirteen cases, ten of which had open sucking thoracic wounds. The missiles producing these wounds were single in 24, multiple in five cases. In three of the five cases two foreign bodies were present, in one case three foreign bodies, and in one case four foreign bodies. They were lodged in the abdomen alone or in the chest and abdomen. It is rather interesting to note that two, three, and four missiles may produce and penetrate through a single wound, and the failure to recognize this fact may result, as in one of our cases, in overlooking an important lesion. In size the missiles varied from small shell fragments to fragments 2.5 cm. in diameter. In one instance a machine-gun bullet was retained.

Shock was a striking feature in the majority of these patients on admission. Profound shock necessitating preliminary shock treatment before operation was undertaken, was present in sixteen cases, a moderate grade of shock in nine cases, little if any shock in four cases. From our operative findings it would appear that hemorrhage—never excessive—was but a slight contributing factor in the production of shock, but that the degree of shock bore a definite relation to the presence of open pneumothorax and to the extent of the lesions of important organs.

*Physical Examination.*—The physical examination in these cases showed the symptoms and physical signs common to penetrating thoracic wounds and to abdominal wounds. In the right-sided injuries, hemothorax if the external wound was closed, or hemopneumothorax if it was open, was invariable in this series. The hemorrhage occurred from the lung alone, from the lacerated liver alone, or from both lung and liver wounds. The usual symptoms of cough, hemoptysis, and dyspnea were present in varying degree. The abdominal signs were those of upper abdominal pain, tenderness and rigidity. But in cases in which a bleeding

liver wound gave rise to an excessive hemoperitoneum, general abdominal rigidity, even a boardlike abdomen, was present. Hiccup and vomiting were infrequent in the right-sided injuries; but occurred when the liver was perforated and additional lesions within the abdomen were produced. Bloody urine was present when the right kidney was injured. In these as well as in the left-sided injuries, the laceration of the diaphragm may actually be seen when the external thoracic wound is large. In the left-sided injuries the same signs and symptoms common to thoracic wounds were present; but the abdominal signs due to more frequent injury to hollow abdominal viscera were more marked. Vomiting, in addition to abdominal pain, tenderness and rigidity, was present in all cases in which hollow viscera were perforated; in part due perhaps to the perforation *per se*, in part no doubt to an early peritonitis from leakage of stomach and intestinal contents. It is remarkable, however, to observe, as in three of our cases of left-sided injury, that the abdominal viscera may entirely escape injury, even when the course of the missile, as determined by the external wound and the location of the foreign body, is such that escape from injury seems impossible.

Herniation of the abdominal viscera through the wound in the diaphragm occurred quite commonly in these injuries. In the right-sided injuries it was uncommon, was always of the liver, and only when the wound in the diaphragm was extensive. In the left-sided injuries, herniation of a bit of omentum was always found in the punctured wounds of the diaphragm. In the large wounds of the diaphragm, herniation of a part of the stomach, the colon, the spleen, or the small intestine occurred. In one case the omentum was prolapsed through the external thoracic wound at the level of the seventh rib. Gastric and intestinal contents were commonly found mixed with the hemothorax when the stomach or intestines were perforated. In one case gastric contents were expelled from a high thoracic wound with each act of vomiting.

The diagnosis of diaphragmatic hernia before operation was possible only in the case of external hernia and in those cases in which the diaphragm could actually be seen through the external wound. In the presence of hemothorax, the diagnosis of diaphragmatic hernia is obviously difficult both by physical and X-ray examination.

*Treatment.*—The treatment of these cases was by operation as soon after admission as their condition warranted it. For the sake of avoiding confusion it may be well to describe the operative procedures separately in the right-sided thoracic wounds, the left-sided thoracic wounds, and the abdominal wounds.

(1) *Right-Sided Thoracic Wounds (17 Cases).*—The wounds of entrance were upon the lateral thoracic wall in eleven cases, upon the anterior wall in three cases, and upon the posterior wall in three cases. The general course of the missiles, therefore, was downward and mesialward in the majority of cases, or backward and downward, or forward and downward. Six were open sucking wounds, eleven were closed wounds. Foreign bodies were localized in the liver alone in six cases, in the lung or pleural cavity alone in two cases, in the abdominal cavity alone in three cases. Multiple foreign bodies were localized in the pleura and liver in two cases, in the pleura and abdominal cavity in one case. In three cases the location of the foreign bodies is not accurately stated. In two cases the wounds were perforating and without retained foreign bodies.

In general the operative procedures in this group of cases consisted of a transpleural exploration, a transperitoneal exploration, or a combined transpleural and transperitoneal exploration. The choice of procedure depended upon the character and position of the external wound and our ability to diagnosticate abdominal lesions. In the presence of open sucking thoracic wounds, these always took precedence and the primary operation was carried out through the thorax, to be followed by an abdominal laparotomy

if conditions warranted. In the low wounds of the back or loin, abdominal exploration was carried out first and followed or not by thoracotomy as seemed indicated. Thoracotomy or transpleural laparotomy was done alone in eleven cases, abdominal laparotomy alone in one case, a combined transpleural and transperitoneal exploration in five cases (primary thoracotomy followed by laparotomy, three cases; primary laparotomy followed by thoracotomy, two cases). Transpleural laparotomy consisted in débridement of the wound of entrance, resection of 10 to 12 cm. of a single rib, exploration of the pleural cavity, evacuation of the hemothorax, removal of missiles and bone fragments from the pleura and lung, débridement and suture of wounds of the lung, incision of the diaphragm in the direction of its fibres, exploration of the liver, removal of the foreign bodies from the liver, and suture of liver wounds. When control of bleeding from the liver was unsatisfactory by suture, tamponade of the liver wound was done, the tampon being brought out through the thoracic wound after suture of the diaphragm to the parietal pleura. The technic of abdominal laparotomy requires no comment. In this series of cases the lesions found were as follows: *Hemothorax* was present in every case, in the majority of slight or moderate grade. The *lung*, aside from small lacerations due to rib fragments or small missiles requiring no special treatment, escaped serious injury in fifteen cases; the lower lobe was perforated in one case; the middle and lower lobes extensively lacerated in one case. Injuries to the *diaphragm* were invariable. The wounds varied from small punctured wounds to lacerated rents 10 cm. in length through which the convex surface of the right lobe of the liver herniated into the pleural cavity. The liver was injured in every case, the wounds being either perforating wounds (2 cases); penetrating wounds with retained missiles (8 cases); or lacerated wounds of the convex surface of the right lobe varying in size up to 10 cm. in length (7 cases). A considerable hemoperitoneum was demonstrated in five cases, but no doubt this condition was present in a larger number of cases. The small intestine was perforated in one case. Closure of the wounds was done without drainage or tamponade in seven cases; tamponade of liver wounds was deemed necessary in eight cases, the tampon being brought out through the thoracic wound; the parietal wounds were drained in two cases. The abdominal cavity was not drained.

*Results.*—Of the 17 patients in this group, nine recovered and eight died, a mortality of 47 per cent. One died upon the operating table, seven died from shock within twenty-four hours of the operation. Of the nine patients who recovered, eight escaped complications and were discharged apparently well. One man developed an infected hemothorax, but recovered after drainage of the pleural cavity.

(2) *Left-Sided Thoracic Wounds (10 Cases).*—The wounds of entrance were upon the left lateral thoracic wall in eight cases, the anterior thoracic wall in one case, and the posterior thoracic wall in one case. The course of the missiles was, therefore, downward and mesialward in the vast majority of cases. Four were large open sucking wounds and one a small sucking wound; five were closed wounds. Foreign bodies were localized in the abdominal cavity alone in eight cases, in the parietal thoracic wall in one case, in the abdominal and thoracic walls in one case. There were no perforating wounds in this group.

The operative procedures were in general similar to those in the preceding group. In open sucking chest wounds, thoracic exploration always took precedence and was followed by laparotomy if indicated. Thoracotomy with abdominal exploration through the diaphragm was done alone in seven cases, thoracotomy followed by laparotomy in three cases. The technic of the procedures was the same as in the preceding group. In two cases incomplete operations were done. In one, owing to the profound shock, nothing more than the operative closure of an open thoracic wound was done, although the likelihood of an

abdominal lesion was recognized. The patient died the day following operation and at autopsy a perforation of the transverse colon with peritonitis was found. In the other a frank operative blunder was made. Two missiles entered the lateral thoracic wall through a single wound of entrance; one apparently was deflected by a rib and was embedded in the muscles of the lateral abdominal wall; one penetrated the thorax. There were signs of abdominal irritation. A thoracotomy was done and the dome of the diaphragm examined. We quite failed to find a wound of the diaphragm and assumed, although we did not find it, that the foreign body was in the pleural cavity. The abdomen was not explored. The patient died of peritonitis, and even at autopsy the wound of the diaphragm was found with difficulty.

The lesions found at operation in this group of cases were as follows: *Hemothorax* was invariably present. In the majority of cases the amount of blood was small. It was macroscopically mixed with stomach or intestinal contents in three cases. The *lung* was extensively injured in two cases; escaped injury in eight cases. The *diaphragm* was invariably injured, the wounds varying from small punctured wounds to large lacerated wounds. In the small punctured wounds a bit of omentum with one exception was found herniated through the diaphragmatic opening. In the larger wounds, a part of the spleen, stomach, or transverse or splenic flexures of the colon in addition to the omentum was found herniated into the pleural cavity. Perforating wounds of the stomach alone were found in two cases, of the colon alone in three cases, of the spleen alone in one case. Two perforating wounds of the lesser curvature of the stomach, together with a grooving lacerated wound of the liver, was found in one case. Operation for abdominal lesions consisted in suture of the perforating wounds of the hollow viscera and splenectomy—in the majority of cases done through the thoracic incision. In only one case was a fibrinopurulent peritonitis present at the time of the operation. In three cases, although the foreign bodies were found lying free in the abdominal cavity, no intra-abdominal injury aside from slight traumatism to the omentum was found. Closure of the wounds was without drainage in six cases, with drainage in four cases.

*Results.*—In this group four patients recovered without complications and were discharged well. Six patients died, a mortality of 60 per cent. Three patients died within twelve hours after operation from shock, two died within thirty-six hours after operation from shock and peritonitis, one died two days after operation from peritonitis. Every patient in this group with the perforation of a hollow viscus died; every patient without the perforation of a hollow viscus recovered.

(3) *Abdominal Wounds (2 Cases).*—The wounds of entrance were upon the anterior abdominal wall just to the right of the epigastric angle in one case, upon the lateral abdominal wall in the other. In the first case the missile coursed upward and to the left, lacerating the concave surface of the right lobe of the liver, perforating the lesser curvature of the stomach, lacerating the spleen, perforating the diaphragm and lower lobe of the left lung, fracturing the ninth rib, and lodging under the skin of the lateral thoracic wall. In the second case, four missiles entered through a single large wound and extensively lacerated the right kidney. One foreign body penetrated the abdominal cavity, three perforated the diaphragm and remained in the right pleural cavity. Operation in the first case, owing to the profound shock, was an incomplete one and consisted of abdominal laparotomy, suture of the liver, suture of the perforation in the stomach, and tamponade of the spleen. The wound in the diaphragm was not treated, nor was the thorax opened. The foreign body was not removed. In the second case operation consisted in a right nephrectomy and an exploratory laparotomy with removal of the foreign body. The thorax was not opened.

*Results.*—Both patients died, a mortality of 100 per cent. In both cases death occurred within twelve hours after operation from shock.

#### SUMMARY

Of the entire series of thirty-nine patients seventeen recovered and twenty-two died, a total mortality of 56 per

cent. Excluding the four patients moribund on admission, the mortality is 46 per cent. Analyzing the results from the standpoint of known injuries to solid and hollow abdominal viscera, we find that the mortality, when solid abdominal viscera alone are injured, is 40 per cent; when hollow abdominal viscera are injured, it is 86 per cent.

## THE NATURAL HISTORY OF TYPHOID FEVER IN BALTIMORE, 1851-1919\*

By WILLIAM TRAVIS HOWARD, JR.

#### INTRODUCTION

In discussions on the course of typhoid fever in any community over a considerable number of years, it has been the custom to assume that there have been, during the periods under study, at least four constants: First, that, on the whole, the population has remained constant in regard to susceptibility to the disease when exposed; second, that both the invasive and the killing capacities of the causal agent have been, on the average, the same; third, that the honesty and the diagnostic acumen of physicians, as well as the available methods of diagnosis and the clinical course of the disease have all remained relatively unchanged; and fourth, that the results of the medicinal treatment and management of cases of the disease have undergone no important variations. As a matter of fact, in most communities at least, such an assumption is unwarranted, and Baltimore is no exception to the general rule that variations in all these factors have taken place between 1851 and 1919, the period covered in the present study.

The population has been under a continual change; one not attributable to loss by death and replacement by birth. New racial elements have entered, and a larger proportion of those born now reach the typhoid age than in former years. Just before our period opens, and running well into its first twenty-five years, there was a large immigration of Irish and of Germans which raised these stocks to a much greater proportion of the population than had obtained previously. Such interesting race stocks as the Russian and Polish Jew, the Czech, the Lithuanian, the Polish, and the South Italian have all joined us since the date when the typhoid rate began to decline. Representatives of other races in smaller numbers have come in more recent times. The numerical proportion of negroes to whites in the population has remained relatively unchanged at one-sixth. Have the immigrants added to or subtracted from the proportion of our typhoid susceptibles? The important questions of the transmission of either typhoid susceptibility or non-susceptibility to the progeny of those who survive attacks of the disease and of the value to be set upon the elimination of typhoid susceptibles through death from this or from other diseases are wholly ignored.

It has been the habit to assume, at least tacitly, that each city has its own typhoid bacillus strain of unvarying infective and lethal capacities. This is far from true, for additions of new races, or strains, of typhoid bacilli are being brought in continually, often from distant parts of the world, and are being diffused; again, old ones are perhaps changing their characteristics or even dying out. It is by no means certain that case fatality rate among typhoid fever cases is in any place, whether it is an open or a closed community, constant over any considerable period of time. In fact, there is much evidence that the contrary is true.

Nor is it possible to estimate accurately the influence of diagnosis, or of fashion in diagnosis, upon typhoid death rates. Bilious fever and malarial fever as causes of death died hard. Pathological anatomists are familiar with the wide margin of error in the diagnosis of typhoid fever. They have found only too often the lesions of this disease and the typhoid bacillus in bodies coming to the autopsy table with diagnoses of pneumonia, empyema, meningitis, tuberculosis (especially general miliary), appendicitis, acute endocarditis, influenza, uræmia, etc., and perhaps the reverse has been experienced as often. Intelligent health officials are well acquainted with these sources of error. In 1919, physicians in Baltimore withdrew the diagnosis of typhoid fever, reported by them to the Health Department, in 42 cases, the most common diagnosis substituted being pneumonia, empyema, influenza, intestinal intoxication, and tuberculosis. Some of these patients had been sent to hospitals by practitioners as cases of typhoid fever. On the other hand, in a considerable number of instances, cases of typhoid fever were first reported as pneumonia or as influenza. Again, it is only comparatively recently that para-typhoid fever has been elevated to the position of a separate disease, and even now while para-typhoid and typhoid fevers, as reported cases, are classified separately in the Health Department records, deaths from the former are still charged to the latter in the international classification.

The question whether the larger experience given physicians during the former period of greater prevalence of typhoid fever did not counterbalance the influence of the more refined methods now available is at best an open one. Outside of exceptionally well organized hospitals, the blood culture method of the diagnosis of typhoid fever is relatively seldom used. Every public health administrator who has carefully

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studied the subject must be aware that, under the conditions which must of necessity obtain in its application and interpretation, the Widal reaction is often a source of error. When a single test is relied upon, many cases of typhoid are excluded, and, in numerous instances, cases of other diseases are classed as typhoid. This is due in the main to three sources of error: the use in the diagnostic laboratories, year in and year out, of a single strain of *B. typhosus*, usually one that is highly sensitive to human serum; the fact that the degree of dilution of the serum is mere guess-work, depending not only upon the bacteriologist's judgment in color, but upon the relative amount of coloring matter in a given amount of the blood of the subject of the test, *i. e.*, his degree of anaemia or plethora; and the fact that in several acute affections, notably influenza, endocarditis, and miliary tuberculosis, which are most apt clinically to be confused with typhoid fever and to suggest to the physician the advisability of appealing to the Widal reaction, the blood serum often acquires the property, even in considerable dilution, of agglutinating *B. typhosus*. These considerable sources of error, while known to many public health bacteriologists, are not so well appreciated by many practising physicians and public health administrators. In a large proportion of the 42 cases of withdrawn diagnosis of typhoid fever above alluded to, the attending physicians were misled by positive Widal reactions. Notwithstanding these drawbacks, the Widal reaction, as applied under the relatively unfavorable conditions inherent to public health laboratory service, is of great service to both practising physician and public health administrator and has undoubtedly promoted accuracy of diagnosis. The laboratory of the Health Department has perhaps been the most effective agent in rectifying the old confusion of malaria with typhoid fever in Baltimore. That some physicians have a habit of burying their fatal cases of continued fever under the diagnosis of typhoid fever is well known in the Health Department. The afflictions sought to be covered under typhoid fever as a cloak are especially puerperal fever, surgical infections, and tuberculosis.

My impression, after four years experience and a study of the records of the Health Department, is that, on account of errors in diagnosis and deliberate misstatements on death certificates, the number of registered deaths from typhoid in Baltimore are certainly below the actual number in the earlier period and probably above it in the later period covered by this study. This is, however, to some degree, balanced by my inclusion of deaths registered as due to typho-malaria with deaths from typhoid fever.

Many facts lead to the conclusion that under the influence of the great improvement in living conditions, using the term in the broad sense to cover improvements in hospitals and in nursing, the substitution of bathing and sponging and of the expectant for the drastic treatment of typhoid fever that has marked the last thirty years, the physician has been able, on the whole, greatly to improve the typhoid patient's chances of recovery.

Though the knowledge necessary for the proper evaluation of these and perhaps other important factors of error is lacking,

attention is directed to them, for, so far as I am aware, in discussions such as the present one, they have been left out of consideration, and it has been very generally assumed as true that the forces of morbidity and mortality of *B. typhosus*, on the one hand, and the material upon which they act, on the other, have remained constant. With the exception of some figures on the white and colored and on the two sexes, there are now available no satisfactory data for a study of the genetic relationships of typhoid fever in Baltimore. This study covers, then, for the most part, a consideration of some of the environmental relationships of typhoid fever in the population of Baltimore from 1851 to 1919, inclusive.

The morbidity and mortality figures, the case histories, and much of the general data were obtained from records of the Health Department, and for these I am under deep obligation to Dr. C. Hampson Jones, Commissioner of Health, Dr. John F. Hogan, Assistant Commissioner of Health, Dr. William Royal Stokes, Bacteriologist, Dr. Marion B. Hopkins, Chemist, Mr. Moore and Miss Betz of the Division of Statistics, and Mrs. Bertha M. Muller. To the Health Wardens and to the Nursing Staff I am indebted for histories of reported cases.

The population figures used in obtaining morbidity and mortality rates are not those of the Bureau of the Census. They were calculated by Mr. John Rice Minor, at the suggestion of Dr. Raymond Pearl, by fitting a logarithmic curve to the population figures of Baltimore, as given by the Bureau of the Census for the census years. These population figures, representing more accurately, it is believed, than those given by the Bureau of the Census, the populations of both census and intercensal years, are used constantly in this laboratory in work on the morbidity and mortality data of Baltimore. As the population figures are somewhat higher than those of the Bureau of the Census, the rates are somewhat lower, particularly in the latter years, than those of the Health Department and of the Bureau of the Census.

#### THE EARLY HISTORY OF THE COURSE OF TYPHOID FEVER IN BALTIMORE

Typhoid fever was not recognized officially by the Health Department as a cause of death until 1851. It was probably hidden under the terms bilious, malarial, typhus, nervous, and gastric fevers, and diarrhoea and dysentery in the early years of the Town and City, and during this period bilious, typhus, and malarial fevers were all accredited with a considerable number of deaths. Nervous fever appears as a cause of death in from 1 to 9 cases in each year from 1812 to 1824. Gastric fever was first given as a cause of death in 1837, and the number of deaths from this affection gradually increased from 3 in 1837 to 30 in 1850, after which this cause declined. Bilious fever was given as a prominent cause of death from 1812, the earliest date to which I can refer, with 99 deaths. It declined to 53 deaths in 1852. It is credited, however, with 72 deaths in 1853. By 1875 it had declined to 1 death and entirely disappeared after 1885.

It is interesting that Thomas H. Buckler, William Power, William T. Howard, Frank Donaldson, Christopher Johnson,

J. W. Houck, Charles Frick, and others, including medical students at the Almshouse, were familiar with the clinical course and anatomical lesions of typhoid fever in the early 40's. Buckler and Power were visiting physicians, and the others mentioned were resident physicians, to the Almshouse and its Infirmary as early as 1843. J. K. Mitchell and other professors of medicine clearly recognized the disease in their lectures and writings in the 40's. It was, however, not until after William Jenner's paper, read on December 11, 1849, before the Royal Medical and Chirurgical Society of London, that the Health Department included typhoid fever as a cause of death. This is the more curious because William Power, generally recognized as the leading clinician of his time in Baltimore, was a pupil of Louis from 1835 to 1838, and was Professor of the Practice of Medicine at the University of Maryland in 1846. Bartlett, who preceded him in the Chair of Practice, was thoroughly familiar with not only the work of Louis, but that of Shattuck in London, Stewart in Glasgow, in 1839 and 1840, and Gerhart in Philadelphia, in 1837, and published his epochal book on continued fevers in 1842. In 1851, Thomas H. Buckler recorded that a very grave form of typhoid fever prevailed among the inmates of the City Almshouse in 1846, 1847, 1848, 1849; that in the latter three years the wards were never free from the fever; and that the resident physicians and students in the Infirmary rarely escaped the disease. Buckler did not mention the degree of prevalence of typhoid fever in the City proper, but he stated that Dr. Frank Donaldson had demonstrated the intestinal lesions of typhoid fever in an immigrant at the Quarantine Hospital in 1847. In the same year, two immigrants with typhoid fever were sent from an immigrant ship to the Almshouse Infirmary. The reports of the Quarantine Officer about this date not infrequently mention cases of typhoid fever.

In the tabulation of the medical and surgical cases treated in the infirmary of the Almshouse in 1828-1829, there were recorded 58 cases, with 13 deaths, of *febris typhoides*. The term *typhoid fever* was first used in the annual report of the Almshouse in 1833, when there were 13 cases and 3 deaths. The annual reports of the attending physicians recorded cases of typhoid fever every year from 1833 to 1849, inclusive, with the exception of 1837. In these seventeen years, there were 359 cases and 106 deaths, with a case fatality rate of 29.53 per cent.

The earliest date of the appearance of the disease in Baltimore is unknown. It was perhaps introduced early and became increasingly prevalent during the enormous growth of the City between 1790 and 1830. It is practically certain that a great many cases of this fever reached Baltimore in the early 40's and early 50's among the great crowds of Irish immigrants who brought typhus and smallpox as well. It is likely that typhoid fever gained a hold in the City at an early date and spread in the usual ways, but especially by pollution of springs and wells and milk and by the mediation of flies, favored by the constant overflowing of the crude privies and privy wells. It is probable that in its earlier days the Lake Roland water supply was not seriously contaminated. With

the increase of the suburban population on this water shed, and later on the Gunpowder water shed, these water supplies became very seriously contaminated. In the meantime, the city springs and wells became more and more polluted, the privies became more dangerous, and milk became a very grave menace.

#### GENERAL SANITARY CONDITIONS IN 1850

In regard to sewers and the disposal of night-soil from privies and privy wells, the foul pictures given in the report of Wynne in 1849 and the reports of the Health Department from this date until a relatively recent period could only be duplicated in the London of the beginning of the 19th century. Harford Run and Jones' Falls to the east and Chatsworth Run and Schroeder's Run to the west duplicated in their foulness the old Fleet and Holborn sewers of London. The Basin into which these filth-streams emptied was perhaps worse than the Thames. It was so foul, that, according to Thomas H. Buckler, as late as 1875 its rotten egg odor commonly reached "Evergreen," his place just north of the present North Avenue, and with a favorable south wind it was clearly detected at Towson. The privies and privy wells in yards and even in the cellars of some of the best houses were constantly overflowing into cellars, courts, lanes, alleys, and streets. The low-lying parts of the City, at Fells Point, along the outlet of Jones' Falls, in the section bordering on the Basin, and the southwest section near Spring Gardens, were in a constant state of nuisance, and large portions of these districts were subject to flooding after very heavy rains. The higher section, with well marked hills and valleys, was far cleaner.

The scavenging and street cleaning were under the control of the Health Department. For this purpose the City was divided into five districts, the cleaning of each of which was let out to separate contractors. The contractor received in payment the street refuse, which he sold as manure, and about one thousand dollars in money. The streets received attention in proportion to their tendency to collect filth, but never more than twice a week, more usually once in two weeks. The numerous narrow alleys and courts, inhabited by the poor, and the depositories of garbage and worse, received little attention and were generally in a filthy condition. The most effective scavenging in these districts was done by swine which were allowed, although it was against the law, to roam through them at their pleasure. The copious showers which were frequent especially in summer, brought about the best results in street cleaning for the City. The streets were often of defective grade and in general roughly paved with cobblestones. There were storm-water gutters on each side, but as sewers were almost non-existent, there being only about two miles of storm-water sewers in the whole City, they led the water through and over streets directly into the Basin or into the nearest stream. With this storm-water went kitchen, bath, and laundry water and much garbage, as well as street manure and material from overflowing privies and cesspools. Between rains these streams were sluggish and in hot weather emitted offensive odors. The garbage and street sweepings

removed by the contractors were dumped on convenient vacant lots at the borders of the City until disposed of.

The night-soil from privies and cesspools was removed by licensed night-soil contractors and sold directly to farmers or manufactured into poudrette. At this time, a portion at least of the night-soil was deposited on the garbage and street manure dumps, and much of its was shipped out of the City on scows.

The nuisances from overflowing privies were a constant source of annoyance and danger to health.

In 1849, not more than one-half, and perhaps not more than one-third, of the population drank water from the public water supply derived from Jones' Falls; the remainder derived its water supply from springs and public and private wells. Many, if not most, of these last must have become grossly polluted by this time from the supersaturation of the subsoil from the numerous cesspools or from surface pollution from privies and overflowing cesspools. It is certain that the public water supply was at this date to some degree polluted from the settlements that grew up around the numerous mills dotting the course of Jones' Falls above the intake.

The better-to-do inhabitants, including the skilled laborers, lived in well built, single-family, brick houses. A considerable portion of the population, consisting mainly of recent immigrants and negroes, lived crowded together in small houses in narrow, dirty, ill-paved, and poorly drained alleys, with an inadequate water supply.

#### SEWERAGE

As previously indicated, at the time at which our period opens, there were no sanitary sewers in the proper sense of the term, and the underground drainage for storm water was very meagre. According to Wynne, in 1849, the aggregate of all the sewers did not exceed two miles in length. Previous to 1862, the few existing storm-water sewers had been put in in a haphazard way.

The first serious consideration of the sewerage question on the part of the City government was in 1859, when a Sewerage Commission was appointed, consisting of Henry Tyson, John Dukehart, and J. Mowton Sanders. In their report rendered in 1862, commonly called the Tyson Report, the Commissioners recommended the establishment of eight sewerage districts, in which sewers were to be built to carry off storm-water and household waste waters, exclusive of human excreta, more readily along the natural drainage lines. Jones' Falls, in which there was an awkward bend to the westward in the neighborhood of Saratoga and Lexington Streets, was to be straightened, and it was proposed that an intercepting storm-water sewer, running parallel to this stream, be built. Some of the recommendations of this Commission, including the straightening of Jones' Falls and the supporting of its walls with masonry, were carried out during the next few years, but no systematic record was kept of the dates and courses of many of the new sewers.

At the invitation of the city government, C. H. Latrobe, C. E., in 1881, made an extensive report on the sewerage ques-

tion. Mr. Latrobe, recognizing that the subsoil had reached the limit of its capacity to care for human excreta by the cesspool and privy systems, recommended a plan for a dual sewerage system: one for surface water and rainfall, to discharge as before into the middle branch of the Patapsco (Spring Gardens), into the Basin, and into the Harbor; and the other for household waste and human excreta, to discharge partly into Middle River (the middle branch of the Patapsco) and partly into the lower harbor below Canton. Relatively very little was done in regard to the storm-water drains, and the recommendations for sanitary sewers were entirely passed over.

Between 1880 and 1890, the construction of storm-water sewers was continued in an irregular way, and Harford, Chatsworth, and Schroeder's Runs were covered over, but in the meantime, there had been a very considerable increase in the number of cesspools draining into the new and the old storm-water sewers which discharged into these runs, or Jones' Falls, or directly into the Basin and into the middle branch of the Patapsco. Many of the sewers, including these runs, were improperly trapped and gave off offensive odors. The uncovered Jones' Falls was, to a very great degree, a combined storm-water and sanitary sewer carrying so much filth that it was constantly necessary to dredge its lower portion for the removal of sediments of organic matter.

A second Sewerage Commission, under the chairmanship of Mr. Mendes Cohen, engaged Messers. Rudolph Hering and Samuel M. Gray as Consulting Engineers and Mr. Kenneth Allen as Assistant Engineer. After an exhaustive study, the Commission, in its report of 1896, recommended a dual sewerage system; the storm-water to be discharged as recommended before, and the domestic waste, including human excreta, to be disposed of by dilution into the deep waters of the Chesapeake Bay, well below the City. Of the two alternative methods proposed by the engineers, *i. e.*, chemical precipitation before such discharge and the use of filtration beds on land in Anne Arundel County, they objected to the former as unnecessary, and to the latter on account of its great expense.

The city government, fearing injury to the fishing industry, particularly on account of the danger of infecting oysters with typhoid bacilli, directed further investigation and a report on the best alternative plan. The Commission then suggested that the plan of land filtration be tried, but be restricted at first to the sewerage from the low level area, thus serving about one-third of the population. The whole matter was then dropped because the people refused to approve a bond issue to pay the cost of the work.

In 1905, the third Sewerage Commission was appointed. Messers. Hering, Gray, and Stearns served as a board of consulting engineers, and Mr. Calvin W. Hendrick was appointed Chief Engineer. Mr. Hendrick and his staff designed and superintended the building of a double system of sewers—surface water and sanitary—covering most of the built up sections of the City. The surface water sewers discharge the storm-water as before. The sanitary sewers carry domestic waste and human excreta to a point on Back River, to the

southeast of the City, where the sewerage is purified and the effluent discharged into the Bay. The system was completed in 1915. Connections were started on a limited scale in the fall of 1911 and were completed in 1917 and 1918. It was estimated by the Chief Engineer that the household sewerage of about 15,000 houses had been discharging into the Basin and Harbor. There are now over 90,000 houses connected, and in most of the old twenty-four wards, the privy and the cess-pool have been eliminated. Thus, the opportunities for fly-borne typhoid must have been greatly restricted.

Much of the sanitary sewerage of a considerable district in the northwest and southwest sections of the City still finds its way into Gwynn's Falls, a stream already polluted with sewerage before it reaches the city limits. As the population so served is still relatively small and the stream is large and rapid, the insanitary conditions are by no means a nuisance comparable to those which obtained in Jones' Falls, or Hartford, Chatsworth, and Schroeder's Runs in former days. Jones' Falls and its tributaries as well still receive a certain but relatively small amount of sanitary drainage from outlying sections of the city. The same may be said in regard to Herring Run, as it runs through the northeastern part of the City. This stream is already seriously polluted from sources to the north of the City. The closely built up Highlandtown, bounding the eastern margin of the City, still retains to a large degree the old, primitive method of storm-water and sanitary sewerage disposal which obtained in the old City before the construction of the new sewerage systems.

#### WATER SUPPLY

From its foundation until 1808, Baltimore depended upon the springs and wells within the City for its water supply, and perhaps to a certain extent, at its borders, upon the several streams. As early as 1792, the legislature gave permission to an insurance company to organize the Baltimore Water Company, with the privilege of supplying water to private users. The Company, however, did not avail itself of this privilege. In 1800, the legislature authorized the Mayor and City Council to introduce water into the City. On account of various delays on the part of the city government, on April 21, 1804, at a public meeting of citizens, a Committee, under the chairmanship of General Samuel Smith, and including John Eager Howard, was appointed to organize a stock company for this purpose. The Company was organized on May 24, 1804.

Jones' Falls having been chosen as the source of supply, a reservoir was constructed near what is now the southwest corner of Cathedral and Franklin Streets, and a wheel and pumps, located at the present site of the Calvert Street Station of the Northern Central Railroad Company, forced water from a common mill race on Jones' Falls, known as Keller's Dam which supplied Salisbury Mill, situated near the site of the old Belvedere Bridge, just east of the present Guilford Avenue Bridge. The main surface pipes were hemlock logs, with bores from  $1\frac{1}{2}$  to 4 inches in diameter, joined by driving the spigot-shaped end of one log into the

bell-shaped end of its mate. The joints were bound with wrought iron bands. The main valves were of cast iron with tapered spigot ends which were driven into the wooden mains, the valves being opened by lifting the valve plugs by means of hooks. The small surface pipes were cedar logs 6 inches in diameter with a 1 inch bore. The first iron pipes laid by the Water Company were imported from England about 1820. The Company supplied the city fire plugs and extended services to private dwellings as and when the revenue to be derived was sufficient to pay the cost and a profit. Service began in 1808. There were always comparatively large areas to which this water supply did not extend, or where it was not taken advantage of, and in which the water of springs and wells was used as in the earlier days.

Somewhat later, the Water Company erected a new pumping station near the old Belvedere Bridge and built an additional reservoir on the high ground at the northeast corner of the present Chase and Charles Streets and a third reservoir called the Mt. Royal Reservoir situated near the present Union Station of the Pennsylvania Railroad. This was supplied by natural flow with water from the mill-race of the Lanvale Cotton Company situated higher up on Jones' Falls. It will be noted that the Water Company did not undertake the construction of dams and large impounding reservoirs along the course of Jones' Falls, but obtained its water supply from the dams of industrial mills which dotted the course of the stream.

John Randel, Jr., in his report to the city government in 1836, recommended that the water be obtained from the Gunpowder River at Great Falls, that for this purpose a dam be built at Tyson's Mills and another across the Western Run, near York Pike, and that, with an aqueduct joining these two sources at Beaver Dam, water be led through the ridge of limestone rock and thence along the western slope of Jones' Falls Creek to a reservoir 300 feet above tide water near Baltimore.

According to Wynne, the service pipes to households, after 1820, were exclusively of lead. In 1849, he estimated that 5000 houses were supplied with hydrants. The City provided free hydrants in certain sections for the poor. At that time the average daily consumption of water was 500,000 to 1,000,000 gallons in the summer and much less in the winter. He describes the water as pure and soft and agreeable to the taste.

The City took over the Water Company in 1852, and after a sharp discussion as to whether the new water supply should be obtained from the Gunpowder River or from Jones' Falls, the contest was decided in favor of the latter. A dam was built at Relay House on the Northern Central Railroad, at an elevation of 220 feet above mean tide. From this, water was led by natural flow through an aqueduct four miles long to a high service reservoir in Hampden and thence by cast-iron pipes for distribution in the City and also to a low service reservoir at North Avenue and the Falls. This system was put into use in 1862. The impounding lake, now called Lake Roland, had an available capacity of 400,000,000 gallons.

The Hampden Reservoir had a storage capacity of 50,000,000 gallons, and the present Mt. Royal Reservoir had a capacity of 30,000,000 gallons.

In 1870, the present Druid Lake in Druid Hill Park, with a storage capacity of 429,000,000 gallons, was completed. Four years later the West High Service Reservoir in Druid Hill Park, with an elevation of 350 feet above mean tide was finished. This reservoir was designed to serve the rapidly growing western and northwestern sections of the City.

In 1862, the consumption of water was not over 8,000,000 gallons of water a day, and it was estimated that the new supply would furnish not under 20,000,000 gallons a day. On account of a severe drought in 1872, the City faced a water famine, and it became evident that the Jones' Falls water supply would have to be reinforced. For this reason, in 1874, a dam was constructed at Meredith's Ford on the Gunpowder River, and 5,000,000 gallons of water a day were forced through a main over the dividing ridge between the Gunpowder River and Jones' Falls into the Channel of Roland Run, a tributary of Jones' Falls, above Lake Roland.

The City then set to work to obtain the larger part of its water supply from the Gunpowder River. In 1875, the following extensive works were begun: An impounding reservoir on the Gunpowder River at Lock Raven with a capacity of 510,000,000 gallons and with a dam 800 feet long and 30 feet high; a gate-house; a supply tunnel 7 miles long, leading to a receiving reservoir at Lake Montebello with a storage capacity of 500,000,000 gallons; and a conduit a mile long from this lake to a gate-house at Clifton, whence a 40-inch main brought water to North Avenue.

The Gunpowder water was turned in direct to the city supply on September 28, 1881. In 1888 an additional storage lake, holding 265,000,000 gallons of water, was built at Clifton.

It would appear that after 1881, under ordinary conditions, at least seven-eighths of the city's water supply was derived from the Gunpowder River and not more than one-eighth from the old Lake Roland supply obtained from Jones' Falls. A comparatively small area in the southeastern portion of the City was supplied up until 1885 by the Baltimore Water and Electric Company.

In 1876, following a very severe and fatal outbreak of so-called typho-malarial fever, but which was probably paratyphoid, Health Commissioner Steuart employed Professor William P. Tonry to make chemical analyses of the water of suspected wells in this locality. The wells were found to be grossly polluted. In 1878 and 1879, Dr. Tonry again examined the water of a number of wells in different parts of the City and condemned a large proportion of them on account of pollution with organic matter. In 1885, he examined the waters of numerous wells in the City for the Commissioner of Health and condemned nearly all of them as grossly polluted. He also made chemical examinations of eight samples of mixed water from the Jones' Falls and Gunpowder River water supplies, taken from the city taps, and found them all suspicious. The Commissioners of Health, between this time and 1888, condemned a large number of springs and wells

within the City and had them closed, so by the time of the annexation in 1888 there were comparatively few remaining wells in use within the then old city limits.

By the annexation of 1888, the City took over, especially on its northern boundary, a large territory rather thickly inhabited, the water supply of which was almost entirely derived from wells and springs. There was an almost complete absence of sewers of any kind in parts of this territory, especially in the Hampden-Woodberry district. In the first year of annexation, 15 cases of typhoid fever occurred in a locality in Woodberry in which the water supply was obtained from a single well. The city water supply was brought into this new territory, and the wells and springs were condemned and abandoned as rapidly as possible. As late as 1897, Dr. Stokes found on examination a large number of polluted wells in the Hampden-Woodberry district.

In 1892, Commissioner of Health McShane established a sanitary inspection of the Lake Roland watershed in order to reduce pollution of the water supply from this source, and in 1896 this inspection was extended to the Gunpowder watershed, and the pollution of these waters from the privies of private dwellings was, to a considerable degree at least, abated. In his report of this year, Commissioner McShane expressed the opinion that the general water supply was seriously polluted.

In this year the chemical and bacteriological laboratories were established in the Health Department, and from this date serious studies of the water supply have been made in both these laboratories.

In general it may be said that chemical and bacteriological examinations made in the Health Department, during this period, of the water of the Gunpowder River and of Jones' Falls and of certain of their larger tributaries, showed an increasingly high degree of pollution, indicated by the presence of organic material and high chlorine content, high colony counts, and the frequent presence of *B. coli*; that there were evidences, both from chemical and bacteriological standpoints, of pollution of the water impounded in the city's reservoirs; and that the water drawn from the city taps showed decided improvement over the reservoir water. In other words, the gross contamination of the water at its source was, to a considerable degree, modified by storage in the city's reservoirs. Dr. Stokes' reports show that there was a rather steady increase in pollution, as judged by the colon bacilli content of samples taken from city taps in 1897 to 1910, inclusive, from 4.5 per cent total samples in 1897 to 57.3 per cent total samples in 1910. He gives the average for the fifteen years, 1896 to 1910, inclusive, as 73.3 per cent of positive colon bacilli findings in 854 samples analyzed. The average bacterial count per cubic centimeter of the tap-water from 1896 to 1902, inclusive, was 600 bacteria. In 1907, it increased to 1300; in 1908, it had dropped back to 600; in 1910, the year of a very considerable typhoid fever epidemic, the average bacterial count per cubic centimeter was 544, and 57.3 per cent of 68 samples examined for colon bacilli were positive. In the previous year, 75 per cent of 112 such samples were positive.

It would appear that a considerable number of wells and springs were still in use in the City as late as 1910, for in this year Dr. Stokes reports the examination of 71 samples of such waters in which colon bacilli were demonstrated in 64.7 per cent.

In a valuable paper published in 1911 on *The Problem of Typhoid Fever in Baltimore*, Dr. W. W. Ford stated that he had examined samples of the Gunpowder River water, over a period of many years, and especially from October, 1910, to June, 1911, and had found high bacteria counts and demonstrated the presence of *B. coli* with great regularity. Ford was able to isolate *B. coli* in the majority of 1 c. c. samples, frequently in 0.1 c. c. and more rarely in 0.01 c. c. samples. He found that other intestinal organisms were also commonly present. The contamination of the water was especially marked in the dry weather of 1910.

As will be seen later, Dr. Jones had reached the conclusion in 1907 that the water must be responsible for at least the majority of typhoid fever cases in Baltimore. Dr. Stokes and Dr. Ford, in their studies of the situation reached the same conclusion in 1910 and 1911.

Purification of the city water supply, through the action of calcium hypochlorite, was begun in June, 1911. The hypochlorite was added to the water of both the Lake Roland and the Gunpowder River supplies at the gate chambers through

TABLE I  
THE LAKE ROLAND SYSTEM

	Average bacteria per c.c.	Percentage of bacterial reduction	Percentage of positive colon tests		
			0.1 c.c.	1 c.c.	10 c.c.
July .....	Raw water...	47,600	....	60	86
	Storage.....	725	99	26	57
	City taps....	4,410	91	0	22
August.....	Raw water...	38,540	....	76	..
	Storage.....	1,210	97	32	66
	City taps....	550	99	3	40
September .....	Raw water...	15,095	....	46	80
	Storage.....	286	98.5	4	31
	City taps....	170	99	6	30
October .....	Raw water...	17,830	....	91	100
	Storage.....	457	99.6	7	37
	City taps....	538	99.5	13	33
November .....	Raw water...	58,045	....	36	91
	Storage.....	627	98.9	0	19
	City taps....	1,430	97.6	4	26
December .....	Raw water...	6,540	....	20	35
	Storage.....	583	91	0	12
	City taps....	642	91.1	5	10

Available chlorine 0.4 parts per million during June and July; 0.6 parts per million during August; 0.75 during September to October 15; 1.0 from October 15 to December 31.

which the water passed from the impounding reservoirs to the city reservoirs. The addition of chlorine to the general water supply was followed by a marked diminution of the amount of bacterial pollution, as shown both by the bacterial counts and percentage of colon bacilli findings. In this year there was also a decided reduction in the typhoid morbidity and

mortality in Baltimore. Stokes, Hachtel, and Freas studied exhaustively the effect of calcium hypochlorite upon the Baltimore water supply in 1911 and published a paper which is an important contribution to our knowledge on the subject (see Tables 1 and 2).

In 1910, the City began to carry out the plans of eminent engineers to increase the Gunpowder water supply by the

TABLE 2  
THE LOCH RAVEN SYSTEM

	Average bacteria per c.c.	Percentage of bacterial reduction	Percentage of positive colon tests		
			1/10 c.c.	1 c.c.	10 c.c.
July .....	Raw water...	60,800	....	62	88
	Storage.....	1,835	97	23	56
	City taps....	1,580	98	12	29
August.....	Raw water...	39,560	....	89	..
	Storage.....	2,497	94	14	48
	City taps....	134	99.5	11	37
September .....	Raw water...	12,409	....	74	..
	Storage.....	754	94.1	14	39
	City taps....	336	95.9	0	33
October .....	Raw water...	4,260	....	82	..
	Storage.....	638	98.6	13	39
	City taps....	596	99	2	33
November .....	Raw water...	120,996	....	55	..
	Storage.....	1,227	99.1	7	20
	City taps....	1,085	99.2	8	38
December .....	Raw water...	19,313	....	29	92
	Storage.....	1,916	90.1	5	22
	City taps....	1,237	93.7	0	12

Available chlorine 0.4 parts per million during June and July; 0.6 parts per million during August; 0.75 during September to October 15; 1.0 from October 15 to December 31.

erection of a higher dam and the creation of a larger impounding reservoir at Lock Raven and to purify this supply by appropriate filters established near the Montebello Reservoir. This work was completed and the filtration plant put into operation on September 15, 1915. At this date, too, the Lake Roland water supply was abandoned, though the works are retained for use in case of emergency. For a few weeks in the winters of 1916 and 1917, on account of necessary repairs to a tunnel, this supply, after heavy chlorination, was used. For at least two years after the new water supply became available, studies in the bacteriological laboratories showed that frequently colon bacilli were present in the water from city taps in 10 c. c. samples, and not infrequently in samples of even 1 or 0.1 c. c. In some months, over 25 per cent of the 10 c. c. samples of tap-water showed the presence of *B. coli*. These findings in the tap-water were often, indeed almost constantly, at variance with the results of the bacteriologist at the water-works. In the last two years, the colon bacillus determinations, obtained in the City Bacteriological Laboratory, have been relatively low. If low colony counts and low percentage of colon bacillus findings mean water free from typhoid bacilli, it is difficult to see that the water can now play any large part as a bearer of typhoid bacilli in the old twenty-four wards of the City. It seems clear that since the

beginning of the use of chlorine purification in 1911, the water supply has become a decreasingly important source of typhoid infection in these wards. Valuable aids to filtration in guarding the city water supply from infection of typhoid bacilli are inspections of the watersheds by the Water Department and the cooperation of the State Board of Health in notifying the Water Department of the presence of reported cases of typhoid fever on the watersheds and in taking appropriate measures to prevent the pollution from them. The map of these two watersheds, separated by a ridge of hills, shows both to be the seat of numerous larger and smaller settlements, many of them villages of considerable size. Inspection shows that many of the smaller, and all of the larger, tributary streams serve as sewers of direct discharge for human excreta from villages, small settlements, and isolated houses and institutions, and that human waste from many dwellings reaches them indirectly from pipes or surface washing. There are a great number of stables for horses and cattle, as well as pigstyes, on their banks, and many stableyards and paddocks straddle the smaller streams. While a great deal has been done in the last few years by the State Board of Health to enforce measures which have decreased the pollution from the larger settlements, it is evident to any thoughtful observer that, unless some unforeseeable revolution occurs in the methods of disposal of human waste, it is hopeless to expect that in any reasonably near time the water from either of these sheds will be safe for drinking purposes without treatment.

#### PAVING AND STREET CLEANING

As early as 1782, grading and paving of the streets and sidewalks was undertaken in a systematic manner, under a special commission appointed by Act of the General Assembly. The work was energetically carried out. The street pavements, at first confined to the business section, were of rough cobblestones, and this character of pavement was in general use until 1911, except where Belgian blocks and occasionally asphalt were substituted on a few business streets and prominent thoroughfares. The report of the City Engineer in that year showed the following street mileage of each material: cobblestone, 354.82; Belgian block, 43.49; sheet asphalt, 19.23; vitrified brick, 19.15; wooden block, 1.63; ordinary macadam, 56.01; bituminous macadam, 2.73; bitulithic, 10.10; cement surface, 2.01; unpaved, 57.73. Much of the better paving had been done in connection with the rebuilding of the section of the City burned in the great fire of 1904.

Since 1912, under the stimulus of Mayor James H. Preston and following the building of the new sewerage system, many miles of streets have been regraded to facilitate surface drainage and paved with smooth pavements. Following this, the greater part of the private alleys, which since the early history of the City had been unpaved or paved with cobblestones and were so rough and irregular as to render drainage and cleaning almost impossible, was brought to proper grade and smoothly paved with substantial material. But for the war, this work would have been completed in most of the old twenty-four wards in 1918.

In the meantime, the Street Cleaning Department had been increased in personnel, equipment, and efficiency for the cleaning of streets and alleys and the prompt removal of garbage. As a result of all these improvements and the practical elimination of the cow stables within the City and the substitution, to a great extent, of the automobile for the horse, the stable and the house fly have been greatly diminished in numbers.

#### MILK AND OTHER FOODS

As in other cities, so in Baltimore, in the early stages of growth, the milk supply was obtained from cows kept in stables and on lots within the city limits. With growth, the neighboring and later, especially with the development of railroads, the distant suburbs were called upon. Speaking by and large, as a natural product, the city and nearby milk were probably of better quality than that from a distance. With city growth and crowding, the feeding of garbage and distillery slop to cows, and the many and rapidly increasing chances of contamination with the microorganisms causing diseases in man, and notably those concerned with diseases of the alimentary tract, especially typhoid fever and dysentery, the city produced milk became not only poorer in quality, but more and more dangerous.

The first recorded investigation of Baltimore's milk is that of Professor Tonry, made at the instance of the Commissioner of Health in 1873. He showed that the best milk came from "dry fed" cows in good stables within the City and immediate suburbs; next stood the farm milk brought in by railroads; and lastly, the milk of the badly stabled, sickly, slop fed cows within the City. Evidence of watering of milk was convincing.

In 1879 an ordinance on milk was passed, making it unlawful to mix water, or any drug, or other article, with milk offered for sale, but there was no provision for its enforcement.

In spite of the recommendations of the Health Department, especially in 1887, when attention was called by the Assistant Commissioner, Dr. McShane, to the milk epidemics of typhoid fever, tabulated by Ernest Hart, no steps were taken by the city authorities to give the Health Department power to control the milk supply until 1894. Soon after the passage by the legislature of an act granting the necessary power, the Mayor and City Council passed an ordinance on May 15, 1894, providing for the inspection of milk and other foods and authorizing the appointment of a chemist and three inspectors. According to the milk standards set by this ordinance, there could be sold in Baltimore only pure, unadulterated, unsophisticated milk, the natural product of healthy cows, not deprived of any part of its cream, and to which no additional liquid or solid or preservative had been added, and which at 60° Fahr. shall have a specific gravity of not less than 1029, total solids, 12 per cent, and butter fat, 3 per cent.

In 1896 an ordinance regulated the ventilation, flooring, and cleanliness of cow stables; required the tuberculin test for milch cattle within the City; and made compulsory the prompt reporting to the Health Department not only of the occurrence of "contagious and infectious" diseases among

cows, but of cases of asiatic cholera, croup and diphtheria, measles, scarlatina, smallpox, typhus and typhoid fevers upon premises with milch cows, or where milk is handled or offered for sale. Milk from premises with cases of any of these or other infectious diseases could not be sold or given away until the Commissioner of Health deemed it safe. Persons connected with dairying and milk handling were forbidden to enter such premises.

By the ordinance of 1902, the sanitary standards under which milch cattle could be kept were made more stringent by requiring non-absorbent floors in stables, with proper drainage and more air space and range for cows, and by forbidding privies, cesspools, and the presence of fowl, swine and horses in stables or connected with rooms where milk and cream were handled.

In 1908, a very sweeping milk ordinance was passed, giving the Health Department complete control over the milk supply, requiring permits for handling milk, dairy farm inspection, the sterilization of utensils, regulation of conditions under which milk could be sold, excluding for sale the milk of slop fed cows, and raising the standard for total solids to 12½ per cent and of butter fat to 3½ per cent. In all respects except one it was a model ordinance, and during the next few years a far-reaching scheme for the sanitary control of milk was put into operation. The weak point of the ordinance lay in its general terms. The regulations made by the Department, especially in regard to sanitary conditions under which milk was handled, sold, and pasteurized, were often successfully contested by certain types of milk dealers as unreasonable, and the Department, which was well and intelligently organized for the purpose, was continuously held up in important details by suits brought to restrain its actions. Conditions, especially in regard to the relation of milk to the spread of communicable disease, were undoubtedly greatly improved. Those concerned in the administration of this ordinance deserve high praise.

Between 1908 and 1916, great changes took place in the milk business, especially in regard to the proportion of milk pasteurized and the attitude of the dealers to the milk problem. In 1917, there was passed an amending ordinance regulating specifically and in detail the important points of administration found impossible of execution under the more general ordinance of 1908. The ordinance of 1917 was passed as drawn by a committee headed by Dr. William H. Welch, and though put into execution under conditions of great disadvantage, it has finally met the best hopes of its authors. It is within the bounds of accuracy to state that all the milk used in the City is reasonably safe from typhoid infection. The great bulk of the milk is pasteurized with fair efficiency, put into bottles or other containers well washed, and, on the whole, if not absolutely sterilized, fairly safe from typhoid infection. The small quantity of raw milk of special grades allowed to be sold has stood the test of experiment without transmitting typhoid fever, and there is every reason for concluding that it is effectually safeguarded. In 1918 and in 1919, no cases of typhoid fever were traced to milk. Certainly

there were no ascertainable milk outbreaks such as so often occurred in previous years.

The new milk ordinance did not go into effect until November, 1917, and, on account of war conditions, it was not possible for many dealers to secure and install pasteurizing and other apparatus until well into 1918. Labor for working the plants and ice for refrigeration were also difficult to obtain. It was not until 1919, therefore, that the real advantage of the administration of the ordinance, as shown in the reduction in bacterial counts of the milk supply, was gained. The results for pasteurized milk as delivered from street wagons are illustrated in Table 3 and in the following figures, expressed in terms of annual Levy rating of bacteria per cubic centimeter for the total milk supply: 1917, 500,000 (1959 samples); 1918, 600,000 (3741 samples); 1919, 67,000 (3899 samples).

TABLE 3  
LEVY AVERAGE OF NUMBERS OF BACTERIA PER C. C. IN SAMPLES OF  
PASTEURIZED MILK (ABOUT 300 MONTHLY) COLLECTED  
FROM WAGONS ON THE STREET

Month	Levy average of numbers of bacteria per c. c.		
	1918	1919	1920
January.....	282,000	56,000	13,000
February.....	475,000	41,000	8,300
March.....	450,000	54,000	15,000
April.....	650,000	52,000	.....
May.....	1,500,000	96,000	.....
June.....	1,200,000	130,000	.....
July.....	1,500,000	120,000	.....
August.....	1,700,000	110,000	.....
September.....	840,000	120,000	.....
October.....	350,000	74,000	.....
November.....	115,000	14,000	.....
December.....	71,000	27,000	.....

Judging from the grossly insanitary conditions under which milk was produced and sold in Baltimore from the earliest times and from the number of milk outbreaks recorded in the reports of the Health Department, it is certain that this article of food has until recently played a very important rôle in the spread of typhoid fever in Baltimore. It is likely that the interference with the watering of milk which attended the enforcement of the ordinance of 1894 was, to a considerable degree at least, responsible for the fall in the typhoid rate during the next few years. It was not, however, until the enforcement of the new ordinance of 1917 that milk, as a vehicle of infection for typhoid fever, was practically eliminated.

Of the other foods than milk, butter, cheese, shell-fish, and vegetables and fruits eaten raw are the only ones of importance, from the practical standpoint, in regard to possibility of carrying typhoid fever infection. Control of these by the Health Department has been limited to preventing those sick with typhoid fever, those attendant upon them, and known carriers from handling food or selling or giving it to others.

No outbreaks of typhoid fever spread by any of these substances have ever been convincingly traced by the officials of

the Health Department, but it is quite probable that by some of these means, notably butter and shell-fish, especially oysters, typhoid infection has been carried here. Instances of the spread of typhoid fever in a large city, in either isolated cases or in epidemic outbreaks, by means of butter, cheese, and vegetables, would in the nature of the case be hit upon only by chance. Vegetables grown on ground fertilized by night-soil were sold in Baltimore for many years and perhaps are now, but there are no observations upon the relation of this circumstance to the spread of typhoid fever in the community. The finding of *B. coli* on such vegetables means nothing in this relation, for it would be strange if this organism were not present on the surface of all vegetables exposed to the soil and not protected by pods like peas and beans. Oysters from polluted waters have undoubtedly been sold in Baltimore and typhoid fever may well have been spread by this means in years past; but the height of typhoid prevalence has not synchronized with the oyster season since 1881.

#### STUDY OF TYPHOID FEVER IN THE HEALTH DEPARTMENT

It now becomes our task to consider, as fully as may be, the studies on typhoid fever made in the Health Department.

The first mention of the etiology of typhoid fever in the Health Department reports occurs in 1875 when Commissioner Stewart attributed this disease and certain others to sewer gas entering houses from imperfectly trapped sewer wells, just as Thomas H. Buckler, in 1851, had blamed the cholera and typhoid fever at the Almshouse on the foul gas of an open cesspool. In 1876, Commissioner Stewart attributed an outbreak of "typho-malarial fever" at Fell's Point to polluted wells and had them closed. Three years later, he ascribed the typhoid fever occurring along Harford Run to the foul condition of that sewer stream. Again, in 1880, he blamed the disease on sewer gas, after his inspectors, who had been sent to visit all houses harboring fatal cases of typhoid fever, reported that they had invariably found full or overflowing privy wells or faulty water closets. As a result of this conclusion, very generally accepted at the time, Dr. Stewart got plumbing inspection established in 1885. In the meantime he had bent every effort to control the nuisance involved in the removal of night-soil. At this time, too, he started routine chemical examinations of the waters of springs and wells, a number of which he had condemned. He also began to question the safety of the general water supply. In 1888, Dr. Stewart closed many wells in the Hampden-Woodberry district of the newly annexed territory on account of pollution, having traced 15 cases of typhoid fever in this district to one well.

Dr. George H. Rohe, in his report for 1890, gave more information concerning typhoid fever in Baltimore than all previous Health Commissioners. After noting the progressively increasing number of deaths during the previous nine years, he pointed out that the great excess of cases in the twenty-first and twenty-second wards was due to the polluted wells in the newly annexed territory and further stated that the sanitary inspectors reported that many residents contracted the disease out of the City, particularly at health

resorts, and that many non-residents were brought into the City to the hospitals for treatment. The truth of the last statement can be vouched for by all who were associated with Baltimore hospitals at that time.

In 1894, typhoid fever together with certain other diseases was made reportable to the Health Department.

Commissioner McShane, in his report for 1895, devoted considerable space to typhoid fever. He recognized that the disease is not contagious in the usual strict sense of the term, but certainly commonly communicated through infected foods and drinks. He recommended that every precaution should be taken to guard the water supply. In this year, the City Chemist attributed 12 cases of typhoid fever in an institution to infected milk, and the epidemic subsided after the milk supply was changed. Dr. McShane also took steps to stop the handling of milk by persons associated with cases of typhoid fever and the sale of milk from premises harboring cases of this disease. He stated in 1897 that, "60 per cent of the cases of typhoid fever, concerning which an intelligent history could be gotten, were infected outside of the City."

In 1899, Commissioner Jones made the first spot map, giving the location of reported cases of typhoid fever and showing that the disease was rather evenly distributed over the City. This point was illustrated in his maps for 1902 and succeeding years. In 1899 and in other years, particularly in his elaborate study of 1907, Dr. Jones reached the conclusion that though flies and milk did play a part in spreading typhoid fever, they could not explain the bulk of the cases for obvious reasons, for too many cases occurred in the months without flies and the cases, in the average years, were too well scattered to be explained satisfactorily by milk infection. He was alive to the importance of this latter means of transmission, however, and recorded three striking milk epidemics: one in 1903 among the workers of a large factory who drank milk supplied to them at luncheon (there were 26 cases with 4 deaths); a second in 1906, an extensive epidemic in the Hampden-Woodberry district; and a third in 1907, a small epidemic of 19 cases.

Contact infection as evidenced by secondary cases in households fell far short, of course, of explaining the great annual visitation. From Dr. Jones' figures, I estimate that in the years, 1904, 1905, 1906, and 1907, somewhere between 7 and 9 per cent of the cases could be classed under this category. Of 2225 cases investigated from the standpoint of out-of-town infection, it was found that 489, or only approximately 22 per cent of the cases had been out of the City. Therefore, nearly four-fifths of the cases could not have received their infections outside of the City. On the other hand, there were still many polluted wells within the City, especially in certain parts, and chemical and bacteriological examinations of the general water supply year by year showed increasing evidences of pollution, in spite of sanitary inspections and nuisance abatements along the watersheds. Dr. Jones concluded that the water was the means through which the bulk of the City's typhoid was spread.

Dr. Jones insisted that there were actually many more cases of typhoid fever in the City than were reported. He estimated that in 1906 and 1907, there must have been between 2000 and 2500, instead of the 1000 to 1400 reported. This was based upon the fact that the number of reported deaths calculated on a 10 per cent fatality basis would give these totals. For instance, in 1907 there were 1420 reported cases and 230 deaths, a case fatality rate of 16.3 per cent; on a 10 per cent fatality basis there should have been 2300 reported cases.

This study of typhoid fever by Dr. Jones in the report of 1907 will always stand out as one of the best pieces of work done in the Baltimore Health Department. The task he set himself was to determine the manner in which the bulk of the typhoid infection took place at that date. Recognizing that there were many sub-sources, important enough in themselves, Dr. Jones after careful and judicious weighing of the available evidence, came to the conclusion by orderly exclusion that typhoid fever in Baltimore was at that time chiefly water-borne. Important evidence in support of this conclusion had been accumulated during the preceding years by the chemist, Dr. Lehmann, and the bacteriologist, Dr. Stokes. For the next three years from 1908 to 1910, Dr. Jones exerted himself on the administrative side, as the records show, to eliminate as much as possible the spread of typhoid fever by subsidiary channels; *i.e.*, household contact, flies, and milk.

If there were space, I should like to point out in detail the value of the studies of Dr. Stokes on the water, particularly in connection with the effects of chlorination and filtration, and the important part he has taken in the whole question of the water supply. Attention should likewise be called to the study of the milk supply and the well directed administration of the details of its control by Drs. Blanck and Hopkins and their assistants in later years, as well as the pioneer work of Drs. Lehmann and Hoffmann, their predecessors. Dr. Jones left the Baltimore Health Department in the fall of 1915, and took charge of the Bureau of Communicable Diseases of the

State Health Department. Here in various ways, particularly in tracing cases reported in Baltimore to sources of infection in the counties of Maryland, and in following up clues, in removing cases from the Baltimore list and crediting them to counties of origin, and vice versa, as determined by the evidence, he continued to play an important rôle in the study of typhoid fever in the City.

Dr. W. W. Ford, in his independent investigations of the milk and water supplies and analysis of the Health Department records of the reported cases and deaths of typhoid fever, confirmed the conclusions of Dr. Jones and Dr. Stokes, and thereby rendered an important public service at a critical time when both the public and the medical profession were apathetic.

In 1909, the mortality rate per 100,000 fell to about 24, the lowest in the recorded history of the City, but in 1910, it jumped to over 42, about the level of 1907. As I have already stated, the treatment of the water with hypochlorite of lime and later with alum in addition was begun in June, 1911, and the typhoid rate again dropped abruptly in 1911 and 1912. Since this period there has been a continuous fall in the rate to the present level (in the old city wards).

But it must be pointed out at the same time, that during this period from 1911 to 1919, other factors besides purification of water by chlorination and filtration have come strongly into play. First in importance perhaps is the doing away with great numbers of privies, a considerable administrative feat on the part of the Health Department, by forcing connections with the new sanitary sewerage system; second, efforts on the part of the Health Department to restrain fly-borne typhoid; third, progress in curbing infection through milk; fourth, education of the public, and to some degree at least, anti-typhoid vaccination; and last, the decline of typhoid in the rural districts, due very largely to the increasing activities of the State Health Department.\*

\* To be continued in the September Bulletin.

## A STUDY OF THE INVALID REACTION<sup>1</sup>

By ESTHER LORING RICHARDS

(From the Henry Phipps Psychiatric Clinic of The Johns Hopkins Hospital)

No class of patients inflicts so much strain on the time, patience and medical wisdom of the general practitioner and the specialist as hypochondriacs; and no class of patients suffers more at the hands of the profession than do these unfortunate members of society. The helplessness of efforts to serve this body of ailing human beings seems due to a persistence in our thinking of what Adolf Meyer has called "the medically useless contrast of mental and physical."

According to the pioneers in "neurasthenia" there was a physical basis not only for all its somatic symptoms, but

also for its "psychic" manifestations which were elastic enough to include every reaction except outspoken major psychoses and organic brain disease. This physical basis was faulty nutrition of the nerve cells with resulting increased fatigability of the nerves *per se*. Later Janet and Freud invented ingenious psychological explanations to account for the "psychic" expressions of "neurasthenia."

In studying the 60 cases of invalidism presented in this paper the writer has had but one idea, and that is to approach each case as a problem by itself, to describe faithfully the facts which it presents, and to study them for the purpose of ascertaining what they mean in the patient's life; in

<sup>1</sup> Abstract from the Archives of Neurology and Psychiatry, 1919, II, No. 4, October, 1919.

what setting of life experiences and constitutional make-up, as well as biological activities, they occur; what opportunities for modification they offer, not only from the standpoint of the individual's metabolism and hygiene, but also from that of his constructive constitutional assets, his adaptive resources, his material for instinctive readjustments. With this aim in view it becomes useless to haggle over what symptoms should be charged up to mind and what symptoms to body.

Fifteen of the 60 patients refused to remain for treatment when told that their exclusive salvation did not lie in a continuance of drug and operative therapy. Of the 45 patients treated 16 were discharged as "well" and have remained so; 25 were discharged as "improved," and four as "unimproved." It was not possible to trace 11 of the "improved," but of the remaining 14, six are completely well, four are back at work in spite of a few complaints, and four have relapsed into their former invalidism. As to the "unimproved," two are well, one is at another hospital, and one cannot be traced. The ages of the group vary from 20 to 72 years. The proportion of females to males is 3 to 1. The average duration of symptoms is 5 years; the average length of their stay in the clinic is 12 weeks.

*Symptoms.*—Their complaints included headache, dizziness, general weakness, nausea, eructation, insomnia, anorexia, etc.

*Examination.*—Every patient was subjected to routine examinations as follows: A general physical examination including a neurological status, an examination of the reproductive apparatus, together with laboratory studies of the urine, blood, etc. These inquiries were supplemented by consultations with other hospital clinics such as the dental, Roentgen ray, electrocardiographic, etc., and by such special investigations as gastric analyses, blood-sugar determinations, blood cultures, etc., according as the facts of the routine examinations or the patient's complaints indicated further research. The psychopathologic data were derived from a record of the individual's mental status, and a study of the facts of his growth and development from childhood with particular emphasis on the constitutional make-up and reaction tendencies.

*Method of Treatment.*—The patient was given a frank report of the various examinations, and invited to think of his incapacitations, not as a disturbance in functioning of some point of visceral strategy from which his symptoms seemed falsely to emanate, but to think of his symptoms as substitutes for reactions to unhappy experiences, thwarted ambitions, petty jealousies, romantic disappointments, an empty and dissatisfied life, a desire to escape marital or domestic responsibilities, etc. Along with education in this concept he was given the benefit of any hygienic lifts suggested by the various examinations, such as attention to the weight curve, hemoglobin, eyestrain, etc. Combined with the physician's conscientious survey of the facts of each case was a ward routine arranged so that the patient got a full and well-ordered day with gymnasium, occupation class, recreation, and leisure for reading, writing letters, etc. It has been

found that these concrete activities not only form a sort of natural bridge between the self-limitations of the invalidism and the return to normal action and interests toward which the patient is headed, but they also restore confidence in his somatic capabilities in general, and especially in certain viscera against which he has so long nursed suspicions of incompetence. He learns that he can eat proteins, carbohydrates and fats without disaster, that he can use his eyes without headaches; and can exercise without fatigue.

No. 18 was a single woman of 33 who since 1904 had suffered from diffuse headaches accompanied by nausea, vomiting, and frequently "falling spells" without loss of consciousness. In 1911 she had to give up work and from that time on had lived the life of a recluse. She had been treated for epilepsy without improvement. On admission the physical, neurological and laboratory examinations were negative.

The patient had been a bed-wetter till 6 years, and was a timid, self-conscious child. She had a narrow, rigid home environment where every normal instinct for recreation, social outlets and the expression of her individuality was repressed by a domineering mother. She reacted to this atmosphere with a feeling of inferiority. She shrank from meeting people, feared to take responsibility and suppressed all interest in the opposite sex. At first headaches and "falling spells" followed some exceptional physical or emotional strain, but from 1910 they occurred irrespective of any unusual event, seeming to represent her only means of getting square with an intolerable home situation.

In discussing matters with her the patient was told that her complaints were the expression of her inner conflicts and dissatisfactions, and that the solicitude and sympathy called forth by her affliction satisfied her natural craving for affection and the expression of her individuality. She was urged to reach out toward new outlets in the cultivation of friends, social interests, recreation and occupation. Since discharge three years ago the patient has had no "falling spells," and but seven or eight headaches a year, none of which have been severe enough to keep her from working eight hours a day.

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# BULLETIN

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## HEALING OF END-TO-END INTESTINAL ANASTOMOSSES WITH ESPECIAL REFERENCE TO THE REGENERATION OF BLOOD-VESSELS

By FLORENCE R. SABIN

(From *The Department of Anatomy, Johns Hopkins Medical School*)

In the spring of 1919 Prof. W. S. Halsted returned to the study of methods of end-to-end anastomoses of the intestine, a subject on which he had worked with Dr. Mall in 1887. At that time Dr. Halsted originated the operation while Dr. Mall had shown that histological studies were not only essential for understanding the processes of repair but could also be made an aid in the developing of surgical technique.

In relation to these studies, Dr. Halsted suggested to the writer that the application of some of the improved methods in connection with vascular injections, as applied to the healing of blood-vessels in these anastomoses, might throw some light on the general problems involved in the healing of intestinal wounds. Having had the privilege of working for many years under the stimulus and guidance of Dr. Mall, and having long known of the pleasure he had taken in this work with Dr. Halsted, it was to me a great gratification to have a share in the study of their problem.

After the first two operations, which were performed by Dr. Halsted, the surgical work was done by Dr. Emile F. Holman, whose analysis of the surgical results will be found in the same number of this journal.

As in the original experiments of Halsted and Mall, the animals used were dogs. The series studied by me comprised 25 dogs, of which 20 were injected, involving 27 anastomoses. Sections were cut from all the injected specimens and from three of the uninjected. All of the anastomoses but one were made in the small intestine, that one being in the large intestine; five were in the duodenum and the rest in the upper part of the jejunum. The animals were killed and the injections made at varying intervals after the operation; in one case the injection was made immediately after the operation; the other animals were injected after intervals of from 1 to 69 days.

The injections were made with India ink, diluted one half and made alkaline with a few drops of ammonia. The cannula was inserted into the superior mesenteric artery and a vent was made in the portal vein. After the blood had been washed out with normal salt solution the ink was introduced and injected at a pressure from 100 to 110 mm. of mercury until the intestine looked quite black, when the opening in the portal vein was clamped for a few seconds to insure filling the capillaries. The entire small intestine was then removed

with all the vessels tied off and placed in 10 per cent formalin for 24 hours, after which the areas of the anastomoses were placed in 80 per cent alcohol. After 2 or 3 days in alcohol longitudinal strips were cut through the anastomoses and cleared by the Spalteholz method, while adjacent strips were embedded in celloidin and cut at varying thickness, from 10 to 100 $\mu$ , and stained in hematoxylin and eosin or erythrosin, in alum cochineal, Mallory's connective-tissue stain, and in toluidin blue. The blocks, cleared by the Spalteholz method, were thoroughly dehydrated by running through graded alcohols, using two changes of absolute alcohol; they were then passed through benzene into oil of wintergreen. If when cleared these specimens are too thick to be readily analyzed, they can be cut thinner with a sharp Gillette blade.

In his histological studies Mall divided the healing of intestinal wounds into four stages: (1) The immediate union of the serous surfaces by fibrin; (2) the destruction of redundant tissue in the flaps; (3) the regeneration of the mucosa and (4) the straightening of the intestine. Both Halsted and Mall found that the union by fibrin could be noted even before the operation was completed, and this proved to be of great importance in eliminating what Mall called a "dead space," for when this space formed, it always filled in with leucocytes. There were two factors in its prevention, first the fibrin, and second, the firmness of the stitches, which Halsted showed must enter the submucosa in order to hold securely.

Mall followed the regeneration of the mucosa at the cut edges which took place during the first three weeks. The results depended largely on the accurate apposition of the different coats, submucosa to submucosa and mucosa to mucosa. He noted the retraction of the muscularis mucosæ and stratum fibrosum at the tip, leaving the submucosa exposed and showed how the epithelium regenerated over this area, soon making glands of the simple embryonic type and then villi. He noted that these newly formed glands dipped down into the submucosa and described the new blood-vessels of the mucosa as simulating the pattern of the vessels of the stomach or at least that of the zone of transition between the stomach and duodenum. Perhaps one of his most interesting points was the showing how the intestine rights itself—that is, how the infolded ends straighten out. In the end-to-end anastomosis, most of the infolded parts are viable and the intestine straightens out in the following manner; the inner sutures pull out and are discarded into the lumen of the bowel, while the outer row of sutures pull out of the submucosa into the muscularis, then through the muscle into the peritoneal cavity. In this process, the silk being tied, is anchored either at a point exactly opposite the site of anastomosis, as in Mall's Fig. 12, or may pull out far to the side as in my Fig. 19. The straightening takes place during the fourth week, when the regeneration of the muscularis mucosæ and the stratum fibrosum takes place.

In following the series which I have studied, the most striking point about the form of end-to-end anastomosis, as it has been developed by Dr. Halsted and Dr. Holman, is the very slight damage to all of the tissues and therefore the

slight amount of regeneration called for. This is of course bound up with the fact that there is practically no interference with the blood supply. This is shown in Fig. 1, which is from an anastomosis in the jejunum taken 21 hours after the operation. Here, as will be seen in the photograph, the apposition is perfect, the infolded parts of the intestine being held firmly by fibrin, since there is no suture at this place. The fibrin shows as a dark streak in the photograph with a triangular mass in the serosal border, and it has practically no infiltration with leucocytes. In no other case in our series has the union by fibrin been as firm as this, for though in all but one of our specimens of the first four days the union was firm enough for physiological purposes, still, in cutting out the blocks it was difficult to draw the knife through the anastomoses without loosening the two infolded parts. It will be noted in Fig. 1 that the mucosa is practically intact, with normal villi except at the tip of the anastomosis where the cut was made, and for a short distance on either side of the apex. In this connection it must be noted again that the method of fixation, depending on the passage of formalin through the entire wall of the gut instead of being injected into the vessels or even poured into the lumen, makes it impossible to avoid some damage to the villi due to post-mortem changes. However, a specimen such as this would call for virtually no destruction of redundant parts and only the tip of the anastomosis would need a regeneration of the mucosa to cover the exposed submucosa. In his studies of gastro-enterostomies in dogs, Flint described a sloughing of the mucosa subsequent to the operation, due to a local cutting off of the blood supply. Dr. Holman's form of suture, running as it does parallel to the largest vessels of the wall, *i. e.*, to the vessels of the fourth order, seem to me to be especially adapted to avoid interference with the blood supply. In the specimen shown in Fig. 1 it is true that the injection mass does not fill the vessels of the villi, but the same is true of this entire intestine and means simply that the injection was not pushed far enough to be complete. This has happened in one or two of our experiments. On the other hand, in Fig. 16 is seen a practically complete injection, with the villi intact to the edge of the suture. This is from a case injected 4 days after operation. The section is cut thick in order to show a wide serosal margin in connection with the new growth of vessels; it has no extravasations and represents very well the average of the injections of early stages and so shows that this form of anastomosis need not produce any localized interference with the blood supply.

In testing out the question as to when vessels cross from one of the infolded flaps to the other, we made some experiments of tying off the vessels of the mesentery of one side and were surprised at the amount of filling of the vessels along the wall of the intestine; thus the tying of one of the radiating vessels of the mesentery, and one vascular loop does not prevent the filling of the vessels of the corresponding wall of the intestine. Whether or not it is possible to make as complete a preservation of the blood-supply, both of the stomach and of the intestine, in a gastro-enterostomy can be very

readily tested by similar experiments with injected specimens, but I am confident that these studies prove the matter in the case of the intestine. Flint indeed pointed out the very close relation between the rapidity of the processes of repair and the amount of damage to the blood supply.

In one of our dogs, the nineteenth in the series, three anastomoses were made. The first was very successful and is shown in Fig. 6. Fifteen days after this operation two more anastomoses were made and the animal was killed the next day. In the case of the third anastomosis, a different operation was done; two presection, stay sutures were laid, then the bowel was cut and sutured with two rows of through and through stitches. At the operation Dr. Holman had difficulty in burying the mucosa, so he re-inforced with five Halsted mattress sutures and several Lambert stitches. During the process the wall of the bowel became blue and at the time of operation Dr. Holman noted the method as unsatisfactory. Histological studies confirmed this judgment. The lumen of the gut contained much blood and sections show a considerable mass of clotted blood adhering to the area of the anastomosis. The villi over the anastomosis showed marked capillary haemorrhages, being, in fact, completely filled with corpuscles. The ink extravasated in the submucosa and around the crypts and did not enter the villi at all. In this case, therefore, there was extensive damage to the walls of the blood-vessels in the infolded area. It is interesting to note, however, that in spite of the unsatisfactory nature of the last operation and the fact that it was the second time the abdominal cavity was opened, there were no signs of a beginning peritonitis when the dog was killed. Another operation done on the thirteenth dog, with Connell mattress stitches around one half of the lumen and an over-and-over continuous stitch for the rest with reinforcing sutures, was also proved to be unsatisfactory by the sections, as they showed considerable damage to the mucosa and a very marked infiltration of the entire infolded musculature with leucocytes.

In the study of the early cases, that is, in those of four days and under, of which there were ten, there were signs that the mucosa was not only intact but that the villi might function. In other words, changes in the epithelium over the villi, which Mingazini has recognized as evidences of the process of the absorption of substances other than fat, were present. Any judgment as to whether these changes are physiological or post-mortem, however, is so dependent on perfect fixation that no stress can be laid on them with a fixation such as one gets in injected specimens, where the lumen is tied off to prevent leakage of the injected mass. Consequently, the following experiment was tried: Dr. Holman made an end-to-end anastomosis of the jejunum of another dog, and five days later a second anastomosis of the jejunum was made. The dog was not fed at all until the second day after the last operation, when he ate an enormous meal of meat, potato and cream. Five and a quarter hours later he was killed and the typical picture of fat absorption was found. The lymphatics of the mesentery, as well as the thoracic duct, were full of chyle. The superior mesenteric artery was in-

jected with 10 per cent formalin to fix the chyle in place; frozen sections were then made through each anastomosis and through other parts of the jejunum and stained with Sudan III. The villi over both anastomoses were shown to be as active in the absorption of fat as was the rest of the wall by the presence of fat in the epithelial cells, in the central lacteals of the villi as well as in the lymphatic vessels of the submucosa. Moreover, the villi over the anastomosis which had been made two days before were as active as those over the anastomosis which had been made seven days previously. Thus there was no interference in the function of the villi in the absorption of fat, nor was there any dilatation of the lymphatics in the submucosa which would have followed had there been an interference with the drainage of the absorbed material away from the wall. The lymphatics in the mesentery opposite the areas of the anastomoses could not be seen owing to an extensive adherence of the omentum which took place after the second operation. A block from the second operation was then embedded in celloidin and the sections showed the typical figures of absorption indicated by Mingazini. The epithelial cells are raised from the stroma, the inner borders of the cells being stretched out but not yet ruptured, except at the tips of the villi, while throughout the stroma of the villi are very many plasma cell. Thus the proof that the operation does not inhibit the function of the villi in absorption is complete. From these studies I think that practically the entire infolded ridge is viable and can function so that there is little tissue that is redundant, and hence exceedingly little early destruction.

In contrast to this is the section in Fig. 3 from a case of an anastomosis in which a Murphy button had been employed. In this case the animal was injected immediately after the operation. This section is from the end of the bowel which was the more damaged and shows four zones, one in which there is destruction of all of the mucosa; second, a zone in which only the bases of the crypts are left; third, an area in which all of the villi are gone, and fourth, the intact mucosa. A part of the damaged wall was inclosed in the button and hence would have sloughed off but there was a considerable area of destroyed mucosa outside of the button, showing that the operation produces an extensive ulcer beside the crushed wall which must slough off with the button. The injection is strikingly poor around this end of the anastomosis, though excellent in the other end where the muscle is more strikingly damaged. The well injected end shows marked extravasations of the injected mass, which follows of necessity from the amount of destruction. In our one case there was no chance to follow the processes of repair, since the dog was killed immediately after the operation; but sections show a great amount of damage to the intestinal wall, for there are haemorrhages in some places, and in others a blocking of the circulation and an extensive recent ulcer which must be repaired.

In following the healing of the series of anastomoses, I shall consider three things: (1) the healing of the mucosa, (2) the

amount of damage to the smooth muscle, and (3) the regeneration of the blood-vessels.

#### MUCOSA

The processes in the regeneration of the mucosa can be followed in a series of photographs in Figs. 1 to 12, representing stages of from 1 to 69 days. As has been seen in Fig. 1, if there is a perfect apposition of the two parts there is very little need for the regeneration of the mucosa. However, it is hardly possible to have the apposition quite as perfect at the cut edge all the way around the lumen of the gut. There is, of course, the well known tendency of the mucosa to roll outward at the cut end, and while tying the last two of the second row of stitches the mucosa must often be rolled in under the sutures and one cannot see the exact apposition. In 4 days, unless there has been an exceptionally wide zone of the submucosa exposed, the entire gap of the submucosa is covered by a layer of simple, cubical epithelium. Flint found that this epithelial covering began to spread across the gap as early as the first day. By the seventh, certainly by the ninth day, as shown in Fig. 4, the gap in the mucosa is bridged by simple glands of the embryonic type as described by Mall, that is to say, with glands with high columnar epithelium and many nuclei, often several rows deep and without any differentiation of the cells.

After the glands have formed, a few short, broad villi begin to appear, as shown in Fig. 5, from an anastomosis 14 days after the operation. In this figure is one conspicuous new villus exactly opposite the very apex of the anastomosis. In this case the apposition has been very perfect. The section is through one of the basal stitches around which is a slight localized reaction of leucocytes and giant cells of the type associated with foreign bodies, but there is not the slightest trace of an inflammatory reaction along the serosal margin of the interned flaps.

At the tip of the anastomosis the characteristic retraction of the muscularis mucosae is very plain. The newly formed glands, of an embryonic type, have grown down into the submucosa between the cut ends of the muscularis mucosae. The glands are, however, not as simple as at first, for there is now a beginning of a differentiation of mucous cells in them. The differentiation of an excessive number of mucous cells in the crypts of Lieberkühn over the infolded area is a constant phenomenon from this time on. It shows especially well in Figs. 11 and 12, 50 and 69 days after the operation, in which the pale areas in the crypts are due to an excessive number of mucous cells. In many cases the crypts come to look like glands of the large intestine. For example, in Fig. 13 we have a photograph of a small area from the mucosa of Fig. 7 in which every cell of the glands in a certain zone is a mucous cell.

Fig. 11 is interesting as showing the fate of these areas of overgrowth of mucous cells. It will be seen in the photograph that there are alternating dark and light areas in the crypts; the light areas are masses of mucous cells showing much vacuolization and marked signs of degeneration, the part of the

cytoplasm next the lumen being almost destroyed, while the dark areas represent zones of young cells with a striking number of mitotic figures. Over these areas there was much mucus in the lumen of the intestine. In Fig. 12 is shown a very extensive area of mucous cells in the crypts covering nearly the entire infolded flap and the wall to the right almost to the edge of the section. It seems that the mucosa functions normally at the start and then differentiates a very great excess of cells secreting mucus; these eventually degenerate and are replaced by new cells. This condition seems to be constant, at least it is present in all of our cases above two weeks. It is interesting to note that this destruction of tissue is not directly due to the operation, rather, it seems to me that the infolded ridges are viable, but there is a late destruction of mucous cells which have developed in excess of the normal number as a result of the operation, and are subsequently destroyed and replaced by new cells as a functional adaptation.

Another point of great interest in connection with the mucosa comes out in Fig. 5, that is, the relation of the glands of the mucosa to the muscularis mucosae. Wherever the muscularis mucosae is broken the glands grow down into the submucosa, provided the area is not infected. At the cut edges, as seen in Fig. 5, the muscularis mucosae is markedly retracted. Immediately after the operation, that is in twenty-four hours, the glands sag into the gap, after which they actively grow down by cell-division. This downgrowth of the glands is interesting in connection with the theory that Brunner's glands develop before the muscularis mucosae forms. Elsewhere the muscularis mucosae and stratum fibrosum seem to make a barrier for the glands.

There are three places where this downgrowth of the glands occurs; (1) at the tip of the anastomosis, as shown in Fig. 5; (2) opposite the outer row of stitches, as seen in Figs. 4 and 6; and (3) opposite the basal row, as seen in Fig. 8. In all of the cases in which the growth was opposite the sutures I feel sure that the muscularis mucosae was simply ruptured by the pull of the stitches; indeed in one case the muscularis has been pulled to a sharp angle and not broken. When the stitch actually pierces the mucosa, an abscess forms, as shown clearly in Fig. 12, where the right hand flap is still infolded, while the left is entirely straight. The position of the inner left suture, which has been cast off into the lumen of the bowel, is indicated by the cavity of an abscess now well walled off, and here there has been no new growth of glands whatever.

In Fig. 6 there is a small cyst at the base of the little group of glands that have grown into the submucosa. The formation of these dilatations is characteristic and was noted by Mall. In the same figure there is a break in the mucosa, associated with the process of the casting off of the inner stitch into the lumen of the gut. Indeed, there are some strands of the silk already within the lumen. This is a case 16 days after the operation. Around the suture there is a reaction characteristic of foreign bodies, consisting mainly of plasmacytoid cells, which are the cells of the connective tissue, identified by Maximow as a special phagocytic group, resting wandering cells, which here become active, together with a few giant cells,

and a few leucocytes. I judge that this reaction, which is not of the acute inflammatory type, has been enough to spread the two muscle coats apart. There is one more interesting point about this reaction, namely, that the cavity in which the stitch lies is lined with simple epithelium. It is not possible to say whether this downgrowth took place immediately after the operation, due to an imperfect union by fibrin, or whether it is secondary to the process of the casting out of the suture. The cells do not look like new cells and in one case, shown in Fig. 10, there is a similar cavity lined with epithelium around one of the basal stitches which must have formed just after the operation. This simple epithelium, lining the cavities of the sutures, develops mucus cells. It seems to me such cysts must be abnormal and they make it worth while to stress the importance of firm apposition of the infolded parts. For instance, a slipping of one of the first line of sutures would bring about such a result, so that the first row should be tied with exactly the same care as the second row. A space like the one in Fig. 6 would probably be completely obliterated in the healing following the casting off of the stitch into the lumen of the bowel; but in the case of a basal stitch like the one in Fig. 10, which will ultimately work its way into the peritoneal cavity, the fate of such a cyst is by no means so clear and therefore must be regarded as a disadvantage.

The sections shown in Figs. 8 and 9 are from the same anastomosis, in fact they are cut from the same block. In Fig. 8 is shown a downgrowth of the glands opposite one of the basal stitches on the left side of the photograph. Just at the left border of the cyst around the suture is a little epithelium, evidently derived from the aberrant glands and not by a downgrowth from the apex of the anastomosis. The other section shows another very interesting result of the rupture of the muscularis, that is, the formation of an extensive compound lymph gland. This lymph node lies opposite a basal suture which was on the right side of the section and has been cast off. The node is exactly like a Peyer's patch, with the same breaking of the muscularis mucosæ and the same rather simple glands above it, although this section is from the duodenum. In this instance I assume that the muscularis mucosæ was ruptured opposite a small lymph follicle and that the injury stimulated the growth of the follicle instead of the glands of the intestine. In fact, the glands are less developed than usual, for in the other section, (Fig. 8) the right border of the infolded area has a completely regenerated, simple epithelium, with almost no glands. This area is on the edge of the lymph node; in fact the dark spot in the center of the area is an injection of lymphoid tissue. The thinness of the epithelium here, in so late a stage (25 days after the operation) may be associated with one of three conditions; viz., the development of the lymphoid tissue may have inhibited the glands, there may have been a secondary break in the mucosa associated with the casting out of a stitch, or there may have been an area of sloughing of the mucosa, such as described by Mall and Flint. I think that the first condition is the most probable one.

In following the repair of the intestine, it is a very interesting point to know the fate of these downgrowths of glands into the submucosa. The constancy of the reaction when the muscularis mucosæ is ruptured without infection indicates that the muscularis is a normal barrier to the excessive growth of the glands. In one of Mall's cases (see his Fig. 11) the growth of the glands was so extensive that he termed them an adenoma. But the reason that such a disturbed balance between two tissues has not led to the formation of adenoma in clinical experience is that the muscularis mucosæ grows down around these new glands and restores them to their normal position in the mucosa.

This is brought out in Fig. 10 from a case 38 days after operation, in which there has been a very deep downgrowth of the glands at the cut edge. This case would have shown a perfect result but for the fact already brought out that the epithelium has grown down to one basal stitch and formed a cyst around it. It is especially interesting as showing the formation of a new muscularis mucosæ. From both cut edges of the old muscularis mucosæ, as well as from the edges of the old circular muscle, bands of muscle are growing to form a new muscularis mucosæ, as is shown at a higher magnification in Fig. 14. In this figure the muscularis mucosæ on the lower margin of the photograph has nearly been completed from the old muscularis mucosæ and from a strand from the circular muscle. Around the base of the glands, shown at the right of the photograph the muscularis mucosæ has been completed from the circular muscle, while the upper border of the mucosa has many bands of smooth muscle cut in cross-section. These accessions of muscle from the old circular muscle coat were seen by Flint in his study of gastro-intestinal sutures.

When the regeneration of the muscularis mucosæ is complete and the anastomosis has straightened entirely, such a small villus as the one shown at the depth of the cleft in Fig. 14 will be restored to its normal position. I have not followed the complete regeneration of the muscularis mucosæ, that is, in all its layers. As is well known, this structure is elaborate in the dog, having an outer longitudinal layer and an inner circular layer with the stratum fibrosum. Besides these layers, longitudinal bands of muscle run out into the villi, so that the villi must have a three-way motion in the lumen of the intestine. In the regeneration I have no stages showing the complete restoration of this elaborate pattern, but there is a new simple muscularis mucosæ in Figs. 11 and 12, 50 and 69 days after the operation. Indeed the tendency to the completion of a muscularis mucosæ is constant and hence it must have an important function. I have tried to test the question whether all of the new muscularis mucosæ comes from preceding smooth muscle or whether there is a differentiation of new muscle cells in the intestine, without being able to solve the question with this material. Certainly almost all of the new muscle I find is connected with the old, and the small masses of isolated muscle along the upper border of the glands in Fig. 14 might well prove in serial sections to be connected with the old musculature. It is hard to

believe, however, that this can be true for the few muscle cells which are found in such a new, small villus as that seen in the same figure.

The regeneration of the muscularis mucosæ begins early; in one case studied 9 days after the operation there were strands of muscle streaming out from the cut end of the muscularis mucosæ at the apex of the anastomosis. It is well under way at 38 days and complete at 50 and 69 days. It is thus restored much more quickly and indeed far more completely than the main muscle coats.

#### SMOOTH MUSCLE

At the beginning of the work I expected to find the most marked signs of injury in the wall of the intestine in the mucosa, and this apprehension was due to the care which the histologist has learned to take in the fixation of intestine in order to secure an intact mucosa. To my surprise, however, the mucosa was strikingly intact, but on the other hand, there were distinct signs of damage to the musculature of the wall and these signs showed in the cases as early as 24 hours after the operation. For example, on the left side of Fig. 1, just at the turn in the muscular coat, there is a shadow. This is due to a deposit of fibrin and to an irregularity in the staining reaction of the muscle. This particular damage, I think, was due to the placing of the clamp by which the intestinal contents were kept from the operative field. The clamp was covered with rubber tubing and placed carefully, but the muscle certainly shows signs of injury.

In a subsequent case, (Dog 25) Dr. Holman placed the clamps 3 to 4 inches from the operative field and adjusted them with the greatest possible care. Sections were then cut through the zone of the clamps and showed slight mottling of the cytoplasm of the muscle, so that I think one may say that it is not possible to place clamps, even covered with rubber, with such care that signs of injury to the muscle may not be detected histologically. This would certainly make it worth while to stress the danger of rough handling of tissues containing smooth muscle.

Fig. 15 shows another striking instance of damage to the muscle. It is from the infolded musculature in a dog killed 24 hours after operation. Otherwise, this case showed a beautiful result with no abnormality except a slight infiltration of leucocytes. The light streak at the upper right corner is a space between the infolded serosal coats, perhaps produced by the knife. The dark band to the left is the much damaged longitudinal coats which have reacted with great intensity to the stain, while the circular muscle occupying the main part of the section is much mottled, the dark transverse band containing nuclei that are all pyknotic. All of the early cases show some damage to the muscle, due in part to clamps, but in part also simply to handling, as in this specimen. The case from which Fig. 15 is taken (Dog 12) is an instructive one. An anastomosis was made with practically perfect results, and 24 days later two anastomoses were made at the same time. The first, shown in Fig. 15, was of the presection type, while the second was with sutures of the

through and through type. The animal was killed in 24 hours and it is very striking that the second operation, that is, the one with through and through sutures, shows very much more inflammatory reaction than the first, giving a good chance to contrast the type of suture that passes through all of the coats with the Halsted type that simply enters the submucosa. The case from which Fig. 15 is taken showed excellent apposition; the wall injected very completely and the only defect was the damage to the muscle, which, being infolded and therefore thrown out of function by position, probably would not do serious harm. This case also brought out another point of interest; at the time the dog was killed there was no peritonitis, though it was the second time the abdominal cavity had been opened. In some other cases when the second operation was made very soon after the first it was followed by adhesions. This is, of course, a common surgical experience. To sum up our results in this regard, in the case of Dog 3 there was a very excellent local result of the anastomosis, as shown in Fig. 7; then after 14 days a second operation was done and the animal killed 8 days later. Following the second operation there was a matting of the loops of the bowel with a firm adhesion of the omentum to the second anastomosis. It was later proved that one suture had slipped, thus fully accounting for the poor result. It was interesting in this case that no difficulty was suspected before the animal was killed. On Dog 25, a second operation was done five days after the first operation and when the animal was killed, two days after the second operation, there was an extensive adhesion of the omentum to the bowel, including both anastomoses and the entire surface of the intervening mesentery which had been handled. Since in this case both anastomoses were excellent (indeed this was the case in which we tested the function of the villi after the dog had eaten an enormous meal), the adhesions probably represented the difficulty, well known to surgeons, of handling the peritoneum before it has entirely recovered from the effects of a first operation. The wall of the bowel was in good condition in this case but the omentum itself was really infected. A third case (Dog 16) was injected three days after an anastomosis had been made, and this animal showed an acute peritonitis. This was the only case with an infection following one operation, and it was especially instructive in showing a very extensive damage to the musculature around the anastomosis. In such a case the damage to the muscle is readily accounted for, but in almost all of our other cases there was very little inflammatory reaction; for example, in Fig. 22, it will be noted that the muscle shows no infiltration of leucocytes at all, the section being taken from a dog which was killed four days after operation. In such cases it becomes interesting to know whether the injury to the muscle is due to direct handling or to damage to the sympathetic cells; therefore, I had sections stained in toluidin blue but could find no marked changes in the ganglion cells. The nuclei are often eccentrically placed, even at the edge of the cell, but there is no disappearance of the Nissl substance. Of course an occasional ganglion occurring near a stitch is entirely destroyed, the nerve cells being re-

placed by connective tissue, but for the most part Auerbach's and Meissner's plexuses do not seem badly injured and I therefore conclude that the striking histological changes in the muscle, as seen in sections, are due to the direct effect on the muscle itself.

The regeneration of the muscle coats is bound up with the process of the pulling out of the stitches and the straightening of the intestine and belongs therefore to a later period, namely the fourth week. The process of straightening of the intestine is an interesting one. In this regard, that is to say, in connection with the ultimate result of the restoration of the intestine to its normal condition, our studies, as far as they go, show a very decided advantage of the end-to-end anastomosis over the end-to-side form. In the one case of the latter, as Dr. Holman has described, there is a decided dilatation of bowel and an obvious stasis of materials in the dilated pouch, while in none of the end-to-end anastomoses was there such a dilatation nor any stasis. Even where the infolded flaps are fairly extensive, as in Fig. 5, there was no sign whatever of any blocking of the lumen.

The straightening out of the wall depends on the fate of the basal stitches, Figs. 7, 8, and 9 representing the most completely straightened wall in our series. In each case one side has straightened out more completely, while the other side is slightly raised by a thickened or possibly by a contracted musculature. The two oldest cases (Figs. 11 and 12) happen to show a less straightened wall. In both the suture has pulled out of the submucosa, through the muscularis, into a thickened serosa and is still holding there with very little cellular reaction. In the one case the suture holds both flaps symmetrically, whereas in the other it holds only one. In the case shown in Fig. 11 the opposite side of the bowel in the gross specimen is almost straight, hence the folding shown in the photograph is a local reaction to one stitch. In the injected specimen shown in Fig. 19, on the other hand, the basal suture has been pulled to the side of the anastomosis, so that the actual site of the anastomosis, which is opposite the depression in the mucosa at the extreme left, is thinner than the adjacent wall. It would seem, therefore, that the position of the sutures, determined perhaps by their firmness when there is little inflammatory reaction, controls the time of the final straightening; but in any event, an infolded wall seems to be no disadvantage, whereas a dilated wall is a distinct abnormality.

As can be seen in most of the later figures, there are ultimate gaps in the musculature, after the sutures have pulled through, that are not regenerated, certainly not during the interval we have studied. The fact that these gaps are localized opposite the six stitches around the lumen of the gut, so that the musculature is not completely isolated around the wall, probably makes them of less functional significance. Certainly, the lack of dilatation of the wall in all of our cases proves that the muscle is not sufficiently weakened by this type of operation to cause any thinning out of the musculature.

#### REGENERATION OF THE BLOOD-VESSELS

The regeneration of the blood-vessels in these anastomoses is one of the most interesting parts of the subject, both in relation to the understanding of the processes of repair in adult tissues and in relation to recent work on the embryological aspects of the vascular system. The development of methods by which it is possible to keep the living blastoderm of a chick under observation during the second day of incubation has made it possible to find out just how the vascular system begins, that is to say, to unravel its fundamental morphology. The blastoderms were first grown on a coverslip in a hanging drop preparation by McWhorter and Whipple who followed Harrison's technique of using clotted plasma. An easier technique, and I think a more valuable one for this particular purpose, is that of Lewis and Lewis, in which the blastoderms are grown in Locke-Lewis solution, which is Locke's solution to which 20 per cent of chicken bouillon has been added.

By this method every stage of the origin of blood-vessels can be seen with great clearness in the area pellucida (Sabin, 1920). Blood-vessels begin by the differentiation of a new type of cell, the angioblast, from mesoderm. Masses of angioblasts are of course the well known "blood-islands" of the early embryologists. This process begins in the embryonic membranes; in the chick, first in the area opaca. After such masses have differentiated in the area opaca they differentiate in the area pellucida, and then in turn in the embryo itself so that there is a progressive differentiation of angioblasts from without inward.

Angioblasts have certain characteristics. Their cytoplasm is denser and more basophilic than mesenchyme and, after fixation in Helly's fluid and staining with azur-eosin, they show the well-known basophilic granules depicted in Maximow's and Danchakoff's figures. These characteristics are, however, not wholly adequate for identifying a single angioblast; but after the first division angioblasts can be distinguished by their tendency to form characteristic clumps, apparently syncytial masses. Mesenchyme cells separate after division, but the angioblasts stay together and soon send out characteristic sprouts by which they join similar masses and form plexuses. These plexuses of solid cells are the forerunners of blood-vessels. The lumen of the vessel forms by the liquefaction of the central part of the cytoplasm to make blood-plasma and this liquefaction may take place in a given mass of angioblasts either before or after it has become a part of a plexus. If it takes place while the clump of cells is isolated, a vesicle is formed. The liquefaction of the cytoplasm has been seen in chains of single angioblasts as well as in the clumps, and hence it is actually an intracellular process; the edges of the masses remain as endothelium.

This method of the formation of blood-vessels is fundamental in the chick; the endocardium of the heart and the entire dorsal aorta behind the head fold can be seen to differentiate *in situ* in the living form by this process; moreover, not only the heart and the aorta but the primary vessels of the embryo

are formed in the same way. It is of course true that both angioblasts and their descendants, the endothelial cells, once differentiated, keep on dividing, so that the primitive vascular system is increased by the differentiation of new cells and the division of the old. It therefore becomes of great importance to know when and where the process of differentiation of new cells to make endothelium ceases. It may then be said that the fundamental morphology of the vascular system has been established and rests on a firm basis as a foundation for the study of vascular problems. On this foundation, it is important to know, even if the normal repair of vessels be from old endothelium, whether there is a reserve, in the adult body in general or in any special place, of undifferentiated mesenchyme cells which can give rise to new angioblasts in the case of repair after destruction of tissues.

In the living chick-blastoderms, I have some specimens of the fourth day of incubation in which there are signs that new angioblasts are still differentiating in the membranes; the chicks themselves have not yet been studied from this point of view. The work of E. R. Clark indicates very strongly that there comes a time in normal growth when the differentiation of new angioblasts ceases. Thus it is clear that the next logical step is to test the question in adult tissues as to whether in the repair of injury all of the new growth of vessels is from preceding endothelium or whether there may be undifferentiated cells in the mesenchyme that may form new angioblasts. It was for this reason that the opportunity to study the healing in intestinal wounds with Dr. Halsted and Dr. Holman was so attractive to me.

The evidence from this study is that, in the healing of intestinal wounds in the adult dog, all of the new growth of vessels is from preceding endothelium. The question has still to be attacked in certain specific areas like the spleen and bone marrow, where the organs are built upon the vascular system in a manner different from that in other organs.

As in the case of the mucosa, the striking point about the Halsted operation is the minimum amount of destruction of tissue and consequently the minimum of repair. This is as characteristic of the vascular system as of the mucosa. In fact the viability of the mucosa is dependent on the lack of injury to the circulation.

Through the work of Mall the vascular system of the dog's intestine is well known. The blood-vessels can best be studied by making complete injections and then observing the results either in thick sections or by stripping the coats apart as membranes. The entire specimen should be fixed in formalin and then placed in 70 per cent alcohol; the coats can best be stripped apart while in 70 per cent or 80 per cent alcohol. Both sections and membranes should then be dehydrated and cleared by the Spalteholz method, which is a very great addition to the technique of studying vascular problems.

One of Mall's great contributions was to show that the vascular patterns in organs are very exact and constant. For the intestine he pointed out that if the superior mesenteric artery is to be regarded as an artery of the first order, the radiating branches in the mesentery are of the second, the arches

are of the third, the series of long, penetrating arteries for the submucosa are of the fourth, while the short arteries from the secondary arches are of the fifth order.

In following the repair of the vascular system, thick sections such as the one in Fig. 18 are cut through the anastomosis: or the wall is stripped apart and cleared by the Spalteholz method, and the pattern is then compared with the normal pattern. In this way one can say with precision that this or that area is a zone of new vascular growth. Thin sections from adjacent blocks can then be studied histologically. I should like to stress the importance of this method as giving precision to the attack of any problem involving a new growth of vessels; that is, the necessity of starting with a knowledge of the normal pattern of the vessels and a method of determining the exact areas of deviation from the normal.

In Fig. 18, which is a thick section adjacent to the one in Fig. 6, there are three striking points in connection with the blood-vessels; first, that the pattern of the vessels of the muscularis, the submucosa and the mucosa, is normal; second, that there is a marked dilatation of both arteries and veins of the submucosa, and a similar dilatation of the capillary plexus around the crypts of Lieberkühn in the mucosa; third, that there is a marked new growth of vessels in the area of the apposed serosal coats. At the very apex of the anastomosis the mucosal vessels are, of course, new and their pattern is unusual, one very large straight vessel being especially conspicuous. The black area just beneath the apex is a suture about to be cast into the lumen of the bowel like the one in Fig. 6.

The dilatation of the vessels of the submucosa and around the crypts in the mucosa is constant; it occurs as early as the first day after the operation, as shown in Fig. 1, in which it is very striking in the basal part of the mucosa. In the mucosa it involves not only the arteries and veins but also the capillary plexus. The amount of dilatation of the plexus of the mucosa in this case (Fig. 1) is strikingly brought out in Fig. 2, which shows a part of the same section taken at the same magnification, the vessels being equally well injected but too small to show in the photograph. A thicker section from this specimen brings out the same dilatation in the vessels of the submucosa. The dilatation persists until late; it is present in all of the specimens up to about 50 days when it is overcome. This dilatation must be either a local functional adaptation of the vascular system or is due to a paralysis of the smooth muscle of the vessels.

In the main the growth of vessels is not general but is limited rather to specific areas. The two constant places are the apposed serosal surfaces, as seen in Fig. 18, and the apex of the mucosa, shown very well in Fig. 20. Otherwise, a new growth of vessels is associated with some accidental occurrence, such as an adherent omentum, a thickening of the serosa near the anastomosis, the organization of the wall of a stitch abscess or certain stresses on the tissues connected with the pulling out of the stitches. The most interesting place to study the regeneration is in the apposed serosal surfaces because it is here that the vessels, old and new, can be

studied with the greatest precision. It is necessary first to know the normal blood supply of the serosa. Besides the penetrating arteries, long and short, which course through it, the serosa normally has no vessels that are particularly its own, but certain long capillaries, belonging to the external longitudinal muscle coat, lie on the outer surface of the muscle, hugging it very closely and serving as serosal capillaries in any abnormality of the serosa. That is to say, some of the long capillaries characteristic of smooth muscle lie within the longitudinal muscle, some on its outer surface. This is well shown in Fig. 2. It is these capillaries which are most involved in this new growth, a point well brought out in two figures from a specimen 4 days after the operation. Fig. 16 shows one half of the interned flap, the other having separated in cutting the block. Along the lower border are seen the new vessels of the serosa, while in Fig. 17 is the actual interned serosal margin dissected from a piece of the same block. Of course this piece includes the longitudinal muscle coat, and if it were from any other part of the intestine it would show simply the well known normal pattern of long capillaries characteristic of smooth muscle. It is thus obvious that by the fourth day there has been a very extensive new growth of vessels in this area all along the interned serosal margin.

The interesting point in regard to this new growth is as follows: In the stages beginning at the second day and extending to the third, fourth, and fifth days after operation, there is a very marked proliferation of the endothelium of these serosal capillaries, as well as of the deeper capillaries of the muscle coats. This same proliferation also takes place in the small arteries and veins, certainly in those of the sixth order. The endothelium of the capillaries and of the vessels of the sixth order, both arteries and veins, returns therefore to the embryonic type of angioblastic masses, with the same characteristic crowding of nuclei, in the zone of stimulus. It would certainly be interesting if one could determine what the stimulus is, most possibly a chemical one; it certainly acts in very specific areas. The old endothelial cells divide until they appear as shown in Figs. 21 and 22, the first one showing such an artery and vein while the second shows a capillary. Fig. 21 is taken from the serosal margin of the case shown in 16, while Fig. 22 is from the interned muscularis. It will be seen that the endothelial nuclei are larger than normal and almost touch each other, while the wall as a whole looks swollen. The nuclei of the capillary look smaller in comparison simply because the drawing is less magnified. In Fig. 21 the lower vessel is the artery, shown by the long transverse nuclei of muscle in the lower part and the row of muscle cells in transverse section in the left; the piling up of the nuclei is perhaps even more striking in the vein. Exactly the same heaping up of nuclei is to be seen when the vessels are cut in cross section, so that there must be an almost continuous layer of endothelial nuclei all around the wall of the vessels. Mitotic figures are easy to find in these stages.

This preliminary division of the endothelial nuclei is the first step in the regeneration of vessels. The second is shown in Fig. 23 from the infolded serosa of the same case. This

represents the new growth, a solid mass of angioblasts from an old vessel of embryonic type. In this figure the old capillary is within the longitudinal muscle and has been injected, as is shown by the black granules of the ink, while from its end is a solid mass of cells which have just reached the serosal margin from which the mesothelial cells have disappeared. There is a mass of fibrin, containing a few cells, at the upper left corner of the figure. The solid mass of angioblasts is just beginning to show a vacuolization of the cytoplasm, like that in the embryo, to form a new lumen. Thus the return of the vessels to the embryonic type is complete; the endothelial cells first divide, then return to the angioblastic type, then give rise to masses of new angioblasts which grow out to form new vessels. These new vessels are at first capillaries, and from these capillaries arteries and veins differentiate.

In one of our cases injected on the fourth day after the operation, we tied off two of the long vessels of the mesentery in order to test out the time when there is an anastomosis of new vessels from one interned flap to the other. The experiment proved that the connection is partial on the fourth day. It is maximal on the eighth or ninth, the fusion being then complete. The mass of angioblasts in Fig. 23 has, however, not yet joined with similar angioblasts of the other flap, nor has the lumen become complete; but such a union of the two masses of angioblasts and the opening of the lumen through these masses of cells, would complete the vascular connection of the two sides. It will be remembered that one of the most characteristic of the properties of angioblasts is their tendency to join similar masses of cells by the process of sprouting to form plexuses.

Thus the process of the formation of new vessels has been followed completely in this one place, for on the first day no change can be seen in the serosal margins, on the second day there is a marked multiplication of the endothelial nuclei of the old vessels—that is of the capillaries and of the small arteries and veins—while by the fourth day there is a growth of new angioblasts from the altered endothelium of the old vessels, some of these masses having developed a lumen and joined with similar masses of the other side. By the ninth day the union of the two sides by new vessels is complete, and there is an extensive pattern of new vessels along the entire infolded serosal margins. In the case of the dog which had a peritonitis, the walls of the anastomosis were infected, and it is interesting to note that these processes of regeneration of the vessels were much retarded.

In Fig. 24 is given further evidence that the lumen of the new vessels arises by the vacuolization of angioblasts. This is from a new vessel which is becoming an artery and has been completely injected, but which shows a lumen as irregular as it can possibly be. Large masses of ink in the lumen are connected with other masses by channels so tiny that only single granules of ink can get through them. No such pattern is ever found in old vessels, the type of lumen in which can be seen in Figs. 21 and 22, but such a pattern would be exactly simulated if the developing vessels of the early chick blasto-

derm, such as are shown in Fig. 23 of my paper in the Mall Memorial Volume (Sabin, 1920) were injected. On the right of Fig. 24 is a vessel cut in cross section showing the same heaping up of the nuclei of the endothelium, while in the center is the edge of an artery showing simply the muscle cut tangentially and not involving the lumen at all. In studying an area showing a large number of new capillaries it is very striking that one can find many capillaries in which the lumen is excessively narrow, allowing but single rows of granules of the ink to pass through them, as in Fig. 24, and this appearance is due, I think, to the fact that the lumen is formed, as in the embryo, by a vacuolization of the cytoplasm. The interpretation of this process could hardly be made from sections and was made by watching the phenomenon in the living chick and following a single mass of solid angioblasts through this process of the liquefaction of the center of the mass to the formation of a vessel lined with endothelium.

There is of course difficulty in getting the evidence from sections to say that not a single angioblast arises independently from the mesenchyme and one must first study with care all of the other types of cells involved. They are of course numerous. Around the abscesses are very beautiful examples of the clasmacytotes or the resting wandering cells of Maximow, also known as the pyrrhol cell of Goldmann and belonging to the class of the macrophages of Evans. In the regenerating tissue, that is to say, in the active phase, these wandering cells are very characteristic, being filled with round vacuoles and showing all the signs of phagocytosis rather than presenting the type of exceedingly irregular vacuolization shown by angioblasts. Secondly, the clasmacytotes are not multinuclear. In point of fact the only cell that can be confused with new angioblasts in this tissue is the giant cell associated with foreign bodies. Such a giant cell might be difficult to differentiate from a mass of angioblasts and I found one which closely simulated the wall of a new vessel. It was long and narrow, one of its nuclei was in mitosis, and it looked much like a chain of angioblasts; it could be shown, however, to be a giant cell, as it was close to one of the stitches, was surrounded by several characteristic giant cells, and what was more important, it showed active phagocytosis, there being two red blood corpuscles engulfed in its cytoplasm besides a large amount of acidophilic debris. Thus, though there may be difficulty in saying that there is not a single newly differentiated angioblast in the material, one may say that no cells looking like angioblasts and wholly disconnected from the old endothelium have been found. Moreover, the marked preliminary transformation of endothelium of the old vessels returning to the angioblastic phase is strong evidence that the new endothelium comes from the old.

The point which seems to me to be of the greatest interest in connection with the new growth of vessels is, that in the zones which are proved to be specific areas of new growth the vessels return to their angioblastic phase and the new angioblasts grow out as solid masses of cells in which a lumen is formed just as the lumen of the vascular system is formed in the embryo by an intracellular process of vacuolization.

In Figs. 19 and 20 are shown the ultimate result of the healing of the vessels. The depression at the left of Fig. 19 is the apex of the anastomosis where the vessels have now returned entirely to the normal pattern, the dilatation being wholly overcome. On the other hand, there has been a marked new growth of vessels in the submucosa throughout the center of the section, due to the stretching of the submucosa by the pulling out of a stitch which now shows within the muscularis to the left of the large vessel crossing the circular muscle coat. There is in all of the anastomoses a considerable alteration from the normal pattern of the vessels of the wall due to a partial isolation of patches of muscle where the continuity has been broken by the pulling of the sutures. In the other section (Fig. 20) there is a striking thickening of the serosa along the border of the section and the apex of the anastomosis to the right is marked by a very unusual vascular pattern. Just beneath the apex is a zone where the muscle has not regenerated and to the left a second such layer of connective tissue containing a very large vessel passing to the submucosa. Both specimens show that the dilatation of the vessels, so marked in earlier stages, has been in the main overcome.

#### CONCLUSIONS

In these studies it has been shown that in the end-to-end anastomosis of intestine the infolding of the wall does not produce any blocking of the lumen, that the infolded parts are viable, and that the mucosa continues to function in absorption, but that there is a very great increase in the number of cells secreting mucus. Ultimately this change in functional adaptation is brought back to the normal by the death of the mucus cells and the regeneration of the mucosa.

It has been shown that wherever the muscularis mucosae is cut or ruptured without the occurrence of an infection, the glands of the mucosa invade the submucosa, often forming cysts there, but that these glands are subsequently restored to the mucosa by the regeneration of the muscularis mucosae which makes a barrier for the glands.

For the smooth muscle, the histological technique shows that its cells are very sensitive to injury and that it is hardly possible to put a clamp on smooth muscle without producing changes that can be recognized under the microscope. It seems to me a very important point that our series of end-to-end anastomoses have produced no dilatation of the wall of the intestine and hence no damage to the musculature sufficient to make it thin out. All of the cases show gaps in the musculature where the stitches pull through, but though this damage is inevitable, the fact that the muscle is syncytial, and that the stitches are limited to six points around the lumen of the gut, seems to limit the amount of destruction to the musculature more than in the end-to-side form of the operation.

In the regeneration of the vascular system it has been shown that the regeneration of the vessels is limited to specific areas where the growth of new vessels is preceded by a change in the endothelium of the old vessels which may be characterized as a return of the endothelium to the original angioblastic type

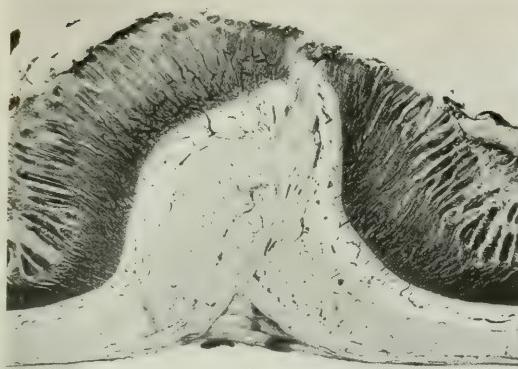


Fig. 1



Fig. 2

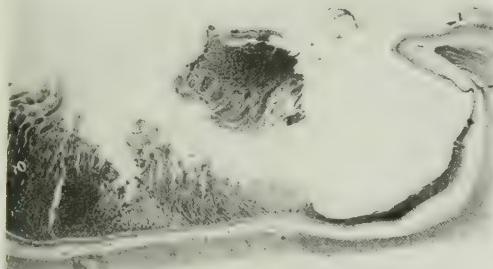


Fig. 3

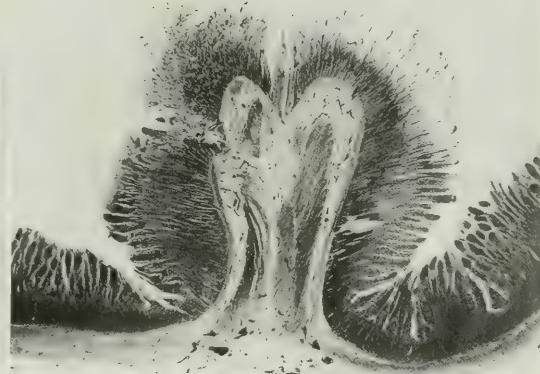


Fig. 4



Fig. 5



Fig. 6



Fig. 7



Fig. 8



Fig. 9



Fig. 10

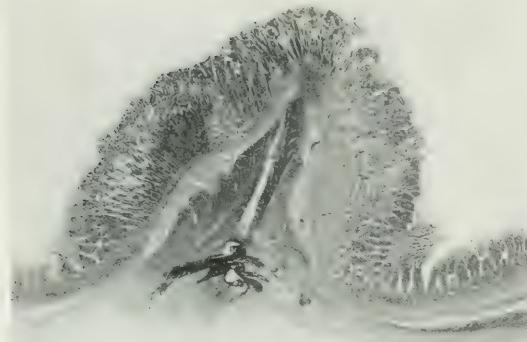


Fig. 11



Fig. 12



Fig. 14



Fig. 19

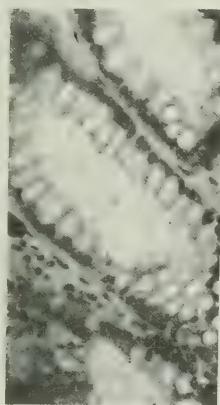


Fig. 13

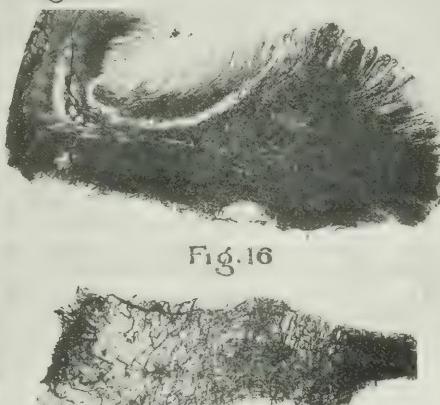


Fig. 16



Fig. 15

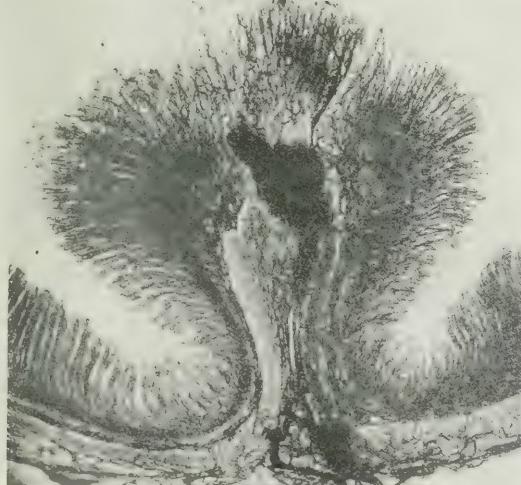


Fig. 18



Fig. 20.

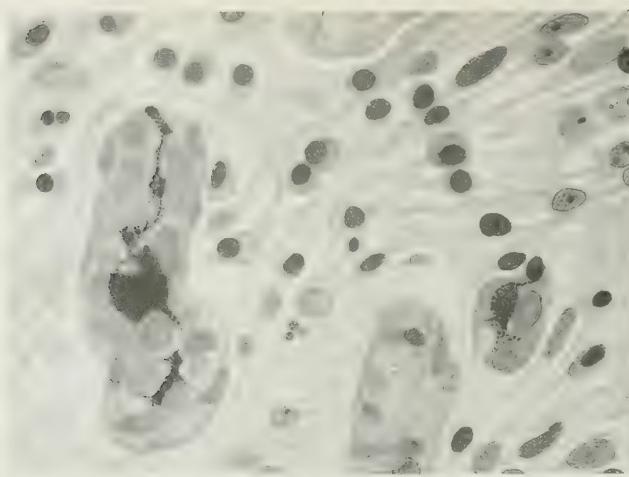


Fig. 24



Fig. 22

J. P. DUDUSCH, Locality



Fig. 23

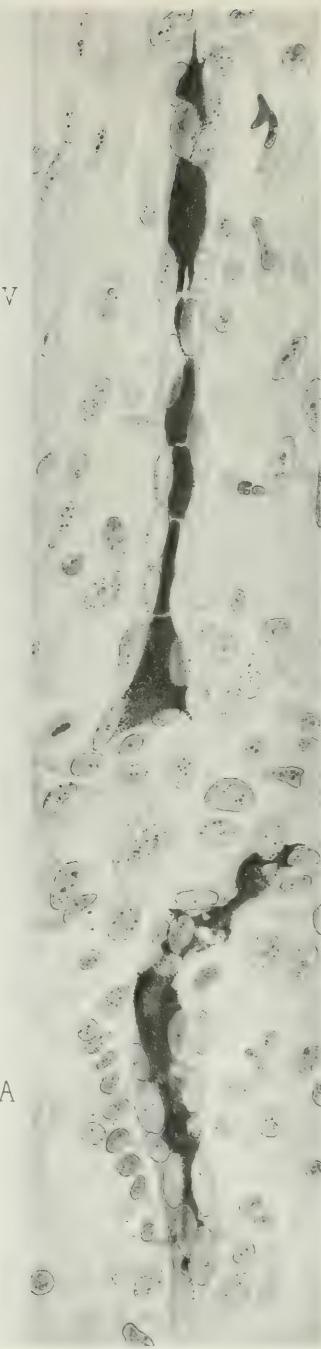


Fig. 21

involving a very great multiplication of the endothelial nuclei, and that from these transformed vessels solid masses of angioblasts like those of the embryo grow out, acquire a lumen, as in the embryo, through liquefaction of the cytoplasm and become new vessels, first capillaries, then arteries and veins.

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- DESCRIPTION OF PLATES**
- FIG. 1.—Section through an anastomosis in the jejunum of a dog (No. 5) injected with India ink 21 hours after operation. It shows an excellent union by fibrin and a marked dilatation of the mucosal plexus of vessels. Stained in cochineal. 100 $\mu$ .  $\times$  10.
- FIG. 2.—Part of the same section as Fig. 1, to show that the undilated mucosal plexus is not visible at this magnification.  $\times$  10.
- FIG. 3.—One end of the intestine after an operation in which a Murphy button had been used. The dog (No. 13) was killed immediately after the operation. It shows a marked destruction of the wall. H and E. 15 $\mu$ .  $\times$  10.
- FIG. 4.—Section through an anastomosis in the jejunum of a dog (No. 9), injected with India ink 9 days after operation. It shows the complete regeneration of the glands of the mucosa at the tip of the anastomosis. H and E. 10 $\mu$ .  $\times$  10.
- FIG. 5.—Section through an anastomosis in the duodenum of a dog (No. 2), injected with India ink 14 days after operation. It shows the regeneration of the glands and the beginning of the new villi at the tip of the anastomosis. H and E. 15 $\mu$ .  $\times$  6.
- FIG. 6.—Section through an anastomosis in the jejunum of a dog (No. 19), injected with India ink 16 days after operation. It shows a stitch in the process of passing into the lumen of the bowel and a downgrowth of the glands opposite a place where

the muscularis mucosæ was ruptured. It is from the same case as Fig. 18. H and E. 15 $\mu$ .  $\times$  8.

FIG. 7.—Section through an anastomosis in the duodenum of a dog (No. 3), taken 22 days after operation. It shows a practically perfect recovery. At the left is a downgrowth of glands opposite a rupture of the muscularis mucosæ. H and E. 10 $\mu$ .  $\times$  10.

FIG. 8.—Section through an anastomosis in the duodenum of a dog (No. 5), taken 25 days after operation. It shows a downgrowth of glands opposite a rupture in the muscularis mucosæ. H and E. 10 $\mu$ .  $\times$  10.

FIG. 9.—Section from the same case as Fig. 8, to show the development of a compound lymph gland opposite a rupture of the muscularis mucosæ. H and E. 10 $\mu$ .  $\times$  10.

FIG. 10.—Section through an anastomosis in the jejunum of a dog (No. 14), 38 days after operation. It shows a deep downgrowth of glands at the apex of the anastomosis. Fig. 14 is a small area of the same section. H and E. 15 $\mu$ .  $\times$  10.

FIG. 11.—Section from an anastomosis in the jejunum of a dog (No. 15), 50 days after operation. It shows a suture still in place holding the infolded parts symmetrically. H and E. 15 $\mu$ .  $\times$  9.

FIG. 12.—Section through an anastomosis in the jejunum of a dog (No. 11), injected with India ink 69 days after operation. A suture still holds one flap infolded and the section shows the crypts transformed entirely into mucus glands. H and E. 15 $\mu$ .  $\times$  8.

FIG. 13.—Glands from the mucosa of the section in Fig. 7, to show how complete the transformation into mucus cells has been. Dog (No. 3), 22 days after operation. 10 $\mu$ .  $\times$  310.

FIG. 14.—Group of glands shown in Fig. 10, magnified to show the development of a new muscularis mucosæ. Dog (No. 14), 38 days after operation. H and E. 15 $\mu$ .  $\times$  40.

FIG. 15.—Section through the infolded musculature of an anastomosis in the jejunum of a dog (No. 12), injected 25 hours after operation, to show the damage to the smooth muscle. H and E. 10 $\mu$ .  $\times$  60.

FIG. 16.—Section of one of the infolded flaps of an anastomosis in the jejunum of a dog (No. 8), injected 4 days after operation. Thick free-hand section, cleared by the Spalteholz method. It shows new vessels along the interned serosal margin.  $\times$  10.

FIG. 17.—Piece of the interned serosa and longitudinal muscle dissected off from a block of the same specimen as Fig. 16, to show the new growth of vessels.

FIG. 18.—Section of an anastomosis of the jejunum of a dog (No. 19) injected with India ink 16 days after operation. Same case as the one shown in Fig. 6. Thick free-hand section cleared by the Spalteholz method.  $\times$  12.

FIG. 19.—Section of an anastomosis made in the jejunum of a dog (No. 5), injected with India ink 25 days after operation. Thick free-hand section cleared by the Spalteholz method. From the same anastomosis as the one shown in Figs. 8 and 9. It shows a suture which, in pulling out of the submucosa, has produced a stretching and a consequent new growth of vessels.  $\times$  5.

FIG. 20.—Section of an anastomosis made in the jejunum of a dog (No. 15), injected with India ink 50 days after operation. Free-hand section cleared by the Spalteholz method. Same specimen as the one in Fig. 11.  $\times$  12.

FIG. 21.—Drawing of an artery and a vein in the interned serosal border of an anastomosis in the jejunum of a dog (No. 8), injected 4 days after operation. It is from the same case as the one shown in Fig. 16. It shows the multiplication of endothelial nuclei which is the first step in the regeneration of vessels. A, artery; v, vein. H and E. 10 $\mu$ .  $\times$  700.

FIG. 22.—Drawing of a capillary in the interned musculature of the same case as Fig. 21 from dog (No. 8), to show the same multiplication of the endothelium preliminary to the growth of new vessels. H and E. 10 $\mu$ .  $\times$  525.

FIG. 23.—Drawing of angioblasts extending from an injected capillary in the longitudinal muscle to the serosal margin, from the same case as in Figs. 21 and 22. Dog (No. 8). *An.*, angioblasts; *cap.*, injected capillary in the edge of the longitudinal muscle coat; *fb.*, fibrin becoming organized between the two serosal surfaces. H and E.  $10\mu$ .  $\times 700$ .

FIG. 24.—New blood-vessels in the serosa adherent to the omentum in an anastomosis of the jejunum of a dog (No. 4), injected with India ink 7 days after operation. The extreme irregularity of the lumen of the vessel to the left shows it to be a new vessel. The injected vessel to the right shows the heaping up of the endothelial nuclei in cross section. H and E.  $10\mu$ .  $\times 1270$ .

## END-TO-END ANASTOMOSIS OF THE INTESTINE BY PRESECTION SUTURES

### AN EXPERIMENTAL STUDY

By EMILE HOLMAN

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Since the days of the "four masters" who lived in the thirteenth century and who pronounced the dried trachea of the goose to be the most suitable and useful adjunct in the repair of the ruptured bowel wall, intestinal suture has been a fascinating study to surgeons, replete in the words of Senn with "stupendous ignorance, clever mechanical ingenuity and patient experimental research."

The following study was undertaken in collaboration with Dr. Sabin at the suggestion and with the generous help and advice of Dr. Halsted. It was our intention to study the regeneration of blood-vessels between the apposed serous surfaces in an intestinal anastomosis, but in the course of Dr. Sabin's careful observations other very interesting details were noted and have been recorded by her in the accompanying article. Similarly, in the development of our operative procedure, modifications were frequently made, resulting finally in a form of end-to-end anastomosis referred to throughout this article as the "presection type." So many and varied have been the methods of intestinal anastomosis described, that it is almost with an apology that this method is offered, but it is given in the hope that it may furnish certain suggestions which may be of value to others in the perfection of an end-to-end anastomosis which will merit adoption.

With the development of intestinal suture have come certain well-defined principles deserving common recognition, but more frequently sinned against than observed in the methods of circular suture now in current use. Briefly stated these principles are:

1. The necessity of depending on an approximation of peritoneal or serous surfaces for a firm and permanent closure. It was in 1802 that Bichat in his *Traité des Membranes* called attention to the absence of adhesions between mucous surfaces and their very frequent occurrence between serous surfaces, but it was not until Lembert's and Jobert's work in 1826 that this observation was applied to intestinal suture, and insisted upon as the *sine qua non* of intestinal repair.

2. The necessity of including in one's stitches a bit of the submucosa or fibrous coat of the intestinal wall, as pointed out by Dr. Halsted in 1887. Textbooks of surgery (*vide* Gould's *Operations on the Intestines*) still speak of "sero-muscular" stitches, whereas it has been sufficiently demon-

strated that such stitches are utterly useless and dangerous, unless they include also a bit of the submucosa.

3. The avoidance of soiling the field of operation by the escape of intestinal contents or by the handling of the mucous coat of the bowel.

4. The necessity in end-to-end union of maintaining the blood supply intact to the edge of the divided intestine. The fear of ischemic necrosis of the turned portion due to pressure on the mesenteric vessels has no doubt been the greatest deterrent factor heretofore in influencing surgeons against the end-to-end suture.

5. The elimination of trauma in performing any intestinal surgery.

These principles have been well observed in the procedures adopted in The Johns Hopkins Hospital for gastro-enterostomy and lateral anastomosis, which is the method most commonly employed clinically in intestinal suture. With particular reference to the last point, Dr. Halsted has long since insisted on the avoidance, in gastro-enterostomy, of approximation clamps which are so liable to inflict injury to the bowel wall. Traction sutures are employed instead, which permit even greater facility in the application of sutures than that afforded by the use of clamps.

With reference to intestinal anastomosis, the great desirability of end-to-end union as compared to lateral anastomosis has been demonstrated so conclusively by the excellent studies of Cannon and Murphy, that we were prompted in our experimental work to employ the circular suture, and so far with excellent results. In 42 end-to-end approximations performed in this laboratory, two subjects developed peritonitis, but both were killed before death occurred. In fact one was killed eight days after the operation, no trouble having been suspected, since the dog was eating normally. All others were sacrificed in good condition, or died of other causes, as, for example, injuries following a fight or an intussusception entirely independent of the anastomosis. Ashton and Baldy recorded a mortality of 30 per cent in their end-to-end approximations and were firmly convinced that only lateral anastomosis should be attempted on the human subject.

Cannon and Murphy's studies were most instructive with reference to the progress of food through the intestine after



FIG. 1.—Drawing illustrating the method of placing the sutures in the presection type of end-to-end anastomosis of the intestine.

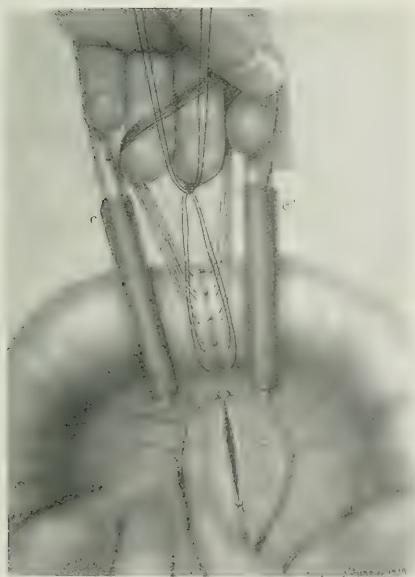


FIG. 2.—Drawing made after the first row of sutures, *b* and *b'* of Fig. 1 have been tied to approximate the mucosal surfaces.

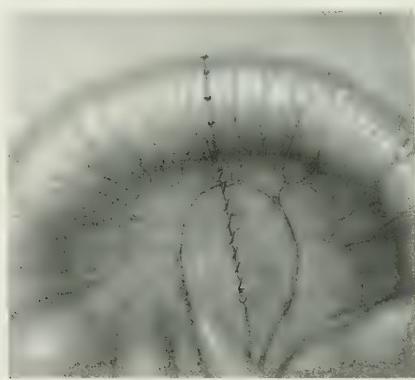


FIG. 3.—Drawing made after the second row of sutures, *a* and *a'* have been tied to approximate the serosal surfaces.



lateral and circular sutures. The experiments were performed on cats with an obviously small lumen of the intestine, and fluoroscopic observations were made following the ingestion of bismuth meals on the first, second, fourth, seventh, and tenth day after the operations.

In no case of end-to-end union was there the slightest evidence of stasis of food in the region of the operation to be observed. The results were quite different with lateral anastomosis. As long as food was passing through the intestine some of it was always present at the point of junction, and when almost all the unabsorbed material was in the colon there still remained a large mass filling the widened lumen where the coils were laterally joined. Observation the next day showed the mass still at the anastomosis. . . . Inasmuch as stasis of the food was not observed at any time after end-to-end union of the severed gut, while after lateral anastomosis the ordinary food was stagnant in the region of the junction, it is clear that, other things being equal, the end-to-end union is to be preferred to the lateral for rapid resumption of the normal functioning of the canal.

In confirmation of these observations circular and lateral sutures were performed on Dog 18, who was killed in a fight 4 months and 6 days after the operation. The specimen obtained was a most interesting one: the circular suture was located proximal to the lateral suture, and was unaccompanied by even the slightest dilatation proximal to the small diaphragm resulting from the inturned bowel. At the point of the lateral anastomosis, however, there was marked bulging of the two blind ends and in spite of an opening 5 cm. long, there was considerable hair and a small marble-sized bit of bone lying in the proximal end, detritus which had passed through the circular suture above. To quote Cannon again:

As to the claim made for lateral anastomosis that it permits the opening between the two intestinal ends to be as large as one may wish, it may be stated that this can be done only by more extensive cutting of the circular muscle of the intestine, thereby still further interfering with peristaltic activity, and also, that the condition to be desired is not such a large opening as an opening that functions satisfactorily.

An interesting observation in this specimen was the absence of de-inversion along the line of suture—the persistence of a diaphragm even after four months. Mall and Halsted, and Grey, noted a straightening of the line of suture beginning as early as the fourth week, resulting finally in complete obliteration of the inturned diaphragm.

Cannon also produced definite evidence of the deterrent influence of trauma and rough handling of the bowel upon the progress of food. Whereas prolonged etherization and cooling or drying of the bowel produced no inactivity of the alimentary canal, manipulation of the stomach and intestine, even gently and under most favorable circumstances, resulted in the absence of any movements of the stomach, with no discharge of food into the intestine, for three full hours after the feeding. Normally a discharge of food from the stomach begins within 20 minutes after ingestion.

Further evidence of the value of gentle handling and lack of trauma is furnished by Dr. Sabin's observations and illustrates well the importance of greater coordination and coopera-

tion between anatomist and surgeon in the interpretation and improvement of surgical experimental work.

Five types of end-to-end anastomosis were performed—in certain instances two kinds in the same dog—but the method finally determined upon as the most satisfactory is the one described as the "presection type."

In Dogs 1, 2, 3, 4, and 5, circular anastomoses were performed by means of Halsted mattress sutures reinforced with Lembert sutures and, although excellent specimens were obtained, these sutures were all placed following the division of the bowel, and therefore with more likelihood of contamination of the operative field. In Dogs 6 to 25 anastomoses of the presection type were performed, in certain cases as high as three sutures in the same dog. In Dogs 12 and 13 anastomoses of the Connell type were also performed. In this type the sutures are placed through all the coats of the bowel and tied within the lumen. Observations recorded at the time of the operation were quite unfavorable as compared with the presection type: the septic interior surface of the bowel was being handled constantly, making asepsis impossible, and the last half of the bowel was sutured with considerable difficulty, due to the eversion of the mucous membrane and to the difficulty of handling the bowel after division.

In Dogs 3, 12 and 19, anastomoses of the plain end-to-end type were performed, similar to that described by Moynihan, in which a running suture through all the coats of the bowel is taken approximating the mucosa, with a second continuous suture approximating the serosa. The same objections apply here as to the Connell type, with reference to the septic surfaces handled, and the difficulty of placing stitches after division of the bowel.

In Dog 13 circular union by means of the Murphy button was established. As early as 1893, Senn stated that any "instrument, suture, or ligature used in effecting the continuity of divided bowel that produces gangrene must be looked upon as a source of danger." As shown by Barbat, the Murphy button is characterized by the sloughing of the inturned portion with ulcer formation, facts sufficient to condemn it, aside from the confirmatory histological observations of Dr. Sabin.

The procedure employed in the presection type is as follows: The two points of proposed division of the bowel are selected at any distance apart, preferably where the vessels of supply are easily seen. The loop to be resected is milked free of intestinal contents, and rubber-covered clamps applied *very gently* and with but just sufficient pressure to prevent the passage of intestinal contents. The clamps are applied on each side of the two lines of division about 1 inch removed from the line of division.

The loop arteries paralleling the bowel are ligated at points *e* and *e'*, exactly opposite the proposed lines of division. The row of *a* sutures is then applied  $\frac{1}{4}$  to  $\frac{1}{16}$  inch removed from the proposed line of division, the first suture being applied at the mesenteric border, and the last on the opposite side also at the mesenteric border. Occasionally, the two may be seen to overlap, thus insuring an adequate approximation at this criti-

cal point. The sutures are applied at right angles to the lumen of the bowel and parallel to the larger vessels coursing over the intestine. They include about  $\frac{1}{8}$  inch of bowel wall with a bit of the submucosa, and are placed about  $\frac{1}{16}$  inch apart, until the whole bowel has been surrounded with a line of interrupted sutures, *a*. A second row of presection sutures, "presection" in that they are applied before any incision into the bowel is made, is taken paralleling the *a* sutures and removed from line of proposed division by only  $\frac{1}{16}$  inch. These *b* sutures are placed exactly opposite the intervals between the *a* sutures, thus ensuring against any leakage between the interrupted stitches.

Two similar rows of *a'* and *b'* sutures are applied at the second line of proposed division, the number of *a'* sutures corresponding exactly to the number of *a* sutures. If the proximal portion of the bowel is dilated, and the distal portion constricted, one may apply the sutures in the constricted portion in a line at an obtuse angle instead of at a right angle to the bowel, and divide the intestine accordingly, thus increasing the size of the opening in the constricted portion.

The main arteries to the loop of the intestine to be resected are then ligated and divided. If these arteries are ligated at the beginning of the operation, the anemia of the bowel wall causes vigorous peristaltic movements which interfere with the placing of the presection sutures. The bowel is divided as closely as possible to the lines of *b* and *b'* sutures, and the intervening portion excised.

The *b* and *b'* sutures are then tied, the two strands of each suture being held and tied as a single thread, each knot, therefore, being made up of four strands of silk. This first line of sutures gives an accurate approximation of the mucosa. The second lines of *a* and *a'* sutures are tied in similar fashion, the two strands of each suture again being held and tied as a single thread. These sutures give an approximation of the serosa around the entire circumference of the bowel, and at the mesenteric border the two adjoining sutures on opposite sides, with an occasional overlapping, ensure an adequate inturn and firm closure at this important point. The rent in the mesentery is closed with continuous or interrupted black silk sutures, care being taken not to include in the stitches any of the vessels supplying the united loops of intestine.

The points of importance to be noted in connection with this suture are:

1. All sutures are applied before incision into the bowel, regardless of the amount of bowel to be resected. The value of this is evident from the point of view of asepsis and from the standpoint of facility in introducing sutures before division of the intestine.

2. All sutures are applied without entering the lumen and without handling the septic mucosa at any time. The method has been applied in the large bowel and in several end-to-side anastomoses in the cecum with excellent results and without subsequent infection.

3. The sutures are applied at right angles to the lumen of the bowel and therefore parallel to the large vessels coursing through the bowel wall. Accordingly, none of the larger

vessels are constricted when these sutures are tied and, as shown by the injections, there is not the slightest impairment of circulation to the severed end of the various intestinal layers. Furthermore, the villi of the mucosa continue to function to the very edge of the divided bowel, as demonstrated by Dr. Sabin in Dog 25. There was also no evidence in a single specimen of sloughing of the inturned edges, ideal and rapid healing at the point of union being thus provided for.

4. In the entire series there was no evidence of dilatation proximal to the anastomosis, thus indicating the absence of any obstructive narrowing of the lumen of the bowel. If this is true for the intestine of the dog with its small lumen, no such difficulty need be expected in the intestine of the human subject with its larger lumen.

5. There is a minimum of trauma such as accompanies the use of mechanical devices, or the handling of the bowel edges with forceps as in the plain end-to-end and Connell sutures, in all of which injury to the mucosa is quite unavoidable. Dr. Sabin's observations illustrate very clearly the importance of avoiding trauma, and as these observations also show that this method is by no means devoid of defects, they will act as an incentive to attempt further improvements in our technique.

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## AN INSTANCE OF VOLUNTARY ACCELERATION OF THE PULSE

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It is a matter of universal knowledge that acceleration of the pulse-rate commonly attends such psychic states as fear, pain and anger. Whatever may be the ultimate source of the stimuli which arouse the pace-maker of the heart to greater activity in such conditions, it is now well established that the immediate control of the heart's rate lies in a delicate balance of influence between two opposing nerve mechanisms—the vagus cardio-inhibitory nerves and the sympathetic cardio-accelerator nerves. Such a balance of influence might be disturbed by certain psychic states through either a reflex stimulation of the accelerator cardiac nerves or a reflex inhibition of the vagi, particularly of the right vagus.

In contrast to the frequent instances of acceleration of the pulse-rate by emotional states, in which the acceleration is reflex and involuntary, voluntary increase of the pulse-rate is very rare. It is possible that emotional states affect the cardiac nerve mechanism reflexly through their influence upon the body as a whole, rather than purely through the discharge of nerve stimuli from the higher to the lower centers. At any rate, the pulse-rate is strikingly immune from control by the will except in a few isolated cases.

West and Savage\* have recently described the fifteenth case of recorded voluntary acceleration of the heart beat. The case reported by these writers was that of a young man whose heart was normal on physical examination and electrocardiography; the subject could voluntarily accelerate his pulse, and the pulse-rate increased by 25 beats per minute following the injection of 0.002 gm. of atropin sulphate. During the strain of voluntary acceleration this subject showed dilatation of the pupils, which has been described in connection with previous cases, and elevation of the blood-pressure. It is not easy, even in a case so carefully studied as that of West and Savage, to state the mechanism by which the acceleration was accomplished: dilatation of the pupils suggests activity of the sympathetic nerves, while marked acceleration from the atropin suggests that the vagus inhibition might be readily lifted.

An instance of voluntary acceleration of the heart beat has recently come to my attention. The subject is a white man, aged 26, single. His general health has always been good, though he has been subject to naso-pharyngeal infections, with lymphatic hypertrophy and glandular enlargement. He has always been an unusually "high strung" individual, excelling in games which require speed and quick muscular con-

trol. For many years he has been subject to attacks of uncontrollable thumping of the heart and tachycardia when under any marked emotion. A few years ago he gave up school for several months and rested, by the advice of physicians, on account of what was called valvular heart disease.

When the recent war broke out, he made three unsuccessful attempts to enlist, but was refused enlistment on account of his heart. He was summoned early in the war before his local draft board, from which he was referred to a medical advisory board, where he came to my attention. Examination revealed a normal heart, with marked tachycardia, and cardio-respiratory murmurs. He was a "high strung" man, and, as the tachycardia was apparently due to excitement, he was accepted. He went through the training without trouble and saw active service, including the Argonne Forest drive. After the armistice, he reported to a medical officer for a minor complaint, and a diagnosis of effort syndrome was made. He was returned to this country, trained in camp, and discharged as well.

He consulted me in October, 1919, not for any particular complaint, but because he was concerned about the diagnosis of effort syndrome, which had been made in the army. He was rather nervous, and having given up exercise on discharge from the army, he was somewhat out of "condition."

Examination showed a man organically sound. The reflexes were moderately exaggerated throughout. He could voluntarily move his ears and posterior scalp muscles. There was marked tachycardia during examination and a sinus arrhythmia. On counting the pulse, I noticed that there was a rapid rise in rate. The patient then gave the voluntary information that he could accelerate the pulse-rate by "thinking about it."

This power to accelerate the pulse voluntarily was readily verified. Almost immediately on command to accelerate, the rise in rate sets in sharply. The pupils dilate slightly, the respirations become somewhat irregular and seem a little more shallow. The subject says that he creates no emotional state whatever, and that the rise in pulse is due to a calm voluntary effort. He is conscious of his heart beat when it is accelerated, and he knows without feeling the pulse whether or not his efforts are strikingly successful. As to the mechanism of the acceleration, his only conviction is that his respirations are not perfectly natural during the effort to accelerate. It will be seen below, however, by pulse tracings, that the acceleration was equally marked when the subject held his breath as it was under the usual conditions.

\* H. F. West and W. F. Savage: Voluntary Acceleration of the Heart Beat. Arch. Int. Med., 1918, XXII, 290.

Several pulse tracings were made by Dr. Donald R. Hooker. The tracings were made at the brachial artery with the Erlanger sphygmomanometer and cuff. The time markings indicate intervals of one second. During the early readings, the subject was rather excited, and the excitement tachycardia made the voluntary acceleration less striking. There was never, however, a failure to accelerate the pulse promptly when the effort was made. The least acceleration per minute was one rise of 20, and the greatest rise was of 40 beats per minute.

Retardation of the pulse-rate seems in all instances to have been a passive one. It was always possible for the subject to approach the initial rate after his effort to retard, but he was not able to retard below the initial rate. In one experiment the patient was ordered to accelerate, and the high speed was maintained for  $1\frac{1}{2}$  seconds. In this case the pulse "got beyond control," because the high rate was held for so long a period, and it fell very gradually when the effort to retard was made. The pulse-rate at the beginning of this experiment was 108; it rose with effort to 131, was sustained for  $1\frac{1}{2}$  minutes, then fell to 117 after 20 seconds. After this, the subject suggested that he be allowed to indicate when he would make the efforts to accelerate and retard: this was done, and the results were somewhat more prompt. A characteristic tracing is shown in Fig. 1.

Electrocardiographic tracings were made by Dr. E. P. Carter. The mechanism of the heart-beat was normal throughout.

The results were as follows:

At rest; sitting. Leads 1, 2 and 3: rate 88, rhythm regular; the P-R interval measures 0.12 second.

No. 2: The R-R interval measures 0.56 second (actual rate 107). Following the signal to accelerate, the R-R interval shortens to 0.48 second (rate 125). Following the signal to retard the R-R interval slows to 0.60 second (rate 100).

No. 4: At rest the R-R interval measures 0.72 second (rate 83); following the signal to accelerate, it shortens to 0.60 second (rate 100) and then to 0.56 (rate 107). Following the signal to slow, the R-R interval drops to 0.72 second (rate 83).

No. 5: At rest the R-R interval measures 0.54 second (rate 111). Inspiration, R-R interval measures 0.64 (rate 93). Acceleration, R-R interval shortens to 0.50 second (rate 120). Retardation, R-R interval lengthens to 0.64 second (rate 93). Expiration, sinus arrhythmia.

No. 6: Right vagus pressure. Before, R-R interval measures 0.68 second (rate 88); afterwards, R-R interval measures 0.64 second (rate 93).

No. 7: Left vagus pressure. No conspicuous change.

*Comment.*—The changes in pulse-rate are not so striking as are those seen in the pulse tracings. The greatest change in pulse-rate by the usual procedure was in No. 4, in which the heart-beats were accelerated by 24 per minute. In No. 5, the effort to accelerate was made while the breath was held in inspiration. The pulse-rate was retarded by 18 beats per minute following inspiration. On effort, with the breath held,

the acceleration amounted to 37 per minute, the retardation to 27 per minute. It is apparent, therefore, that acceleration of the pulse was more marked while the breath was held in inspiration than it was under usual conditions.

Pharmacologic tests were not made, owing to the subject's unwillingness to submit to them. He stated that he was very susceptible to the effect of any drug, especially to that of belladonna. Some years ago he was prostrated by taking capsules containing a small amount of belladonna. He is uncertain as to his exact symptoms at that time, but thinks that he suffered from palpitation and a weak pulse.

The explanation of the phenomenon with which we are dealing is not easy and must be purely hypothetical. The evidence at hand is as follows:

1. "High strung" individual, with highly developed voluntary muscle control.
2. Marked emotional tachycardia.
3. History of sensitiveness to belladonna.
4. Statement of patient that the respiration is in some way involved in the process of acceleration.
5. Marked acceleration with the breath held.
6. Sinus arrhythmia.

The last four of these items rather suggest that the acceleration in the individual may be brought about because of an unstable vagus control of the heart beat, allowing the accelerator influences to gain control at times. It is known that sinus arrhythmia is due to rhythmic changes in vagus activity occurring during respiration. Our subject showed marked slowing of the pulse following his holding the breath in inspiration. However, when the effort to accelerate was made, with the breath still held, there was a sharp accelerator response; slowing took place at will with the breath still held. We might interpret these phenomena as signifying: (1) Slowing from vagus following deep inspiration; (2) acceleration from accelerator (sympathetic) activity with the vagus quiescent; (3) slowing from release of accelerator activity; (4) sinus arrhythmia from rhythmic activity of the vagus as the subject resumes breathing. The patient's feeling that his respiratory movements are linked in some way with the process of acceleration and the observed irregularity of breathing suggest that vagus activity may be minimized by such procedure. The patient's history of sensitiveness to belladonna, if reliable, is strong evidence in favor of his having a vagus system which may be readily neutralized, thus allowing accelerator stimuli to gain control of the beat's rhythm.

West and Savage were of the opinion that in their case the voluntary acceleration of the heart-beat was brought about through a primary decrease in vagus inhibition, probably augmented at times by accelerator influences. Although it is difficult to draw conclusions from our case, there is nothing which could conflict with this hypothesis of West and Savage, and all the evidence would tend to substantiate such a conception of this unusual phenomenon.



FIG. 1.—Brachial Pulse Tracing. Time intervals 1 Sec.

Velocity

Retard

Rate 136

Rate 102

Rate 96

Rate 96

Retard

Rate 136

Rate 102

Rate 96

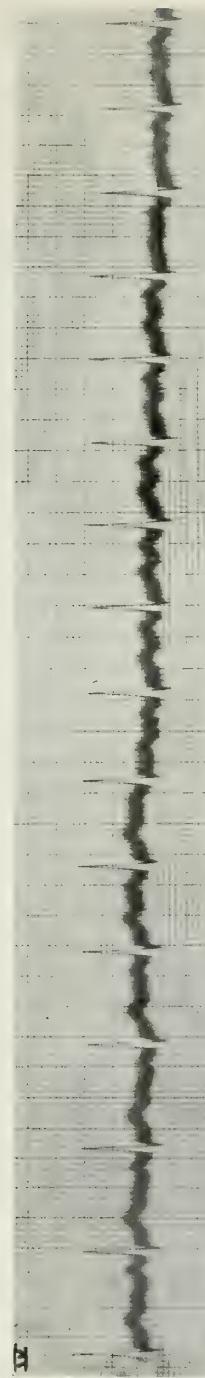
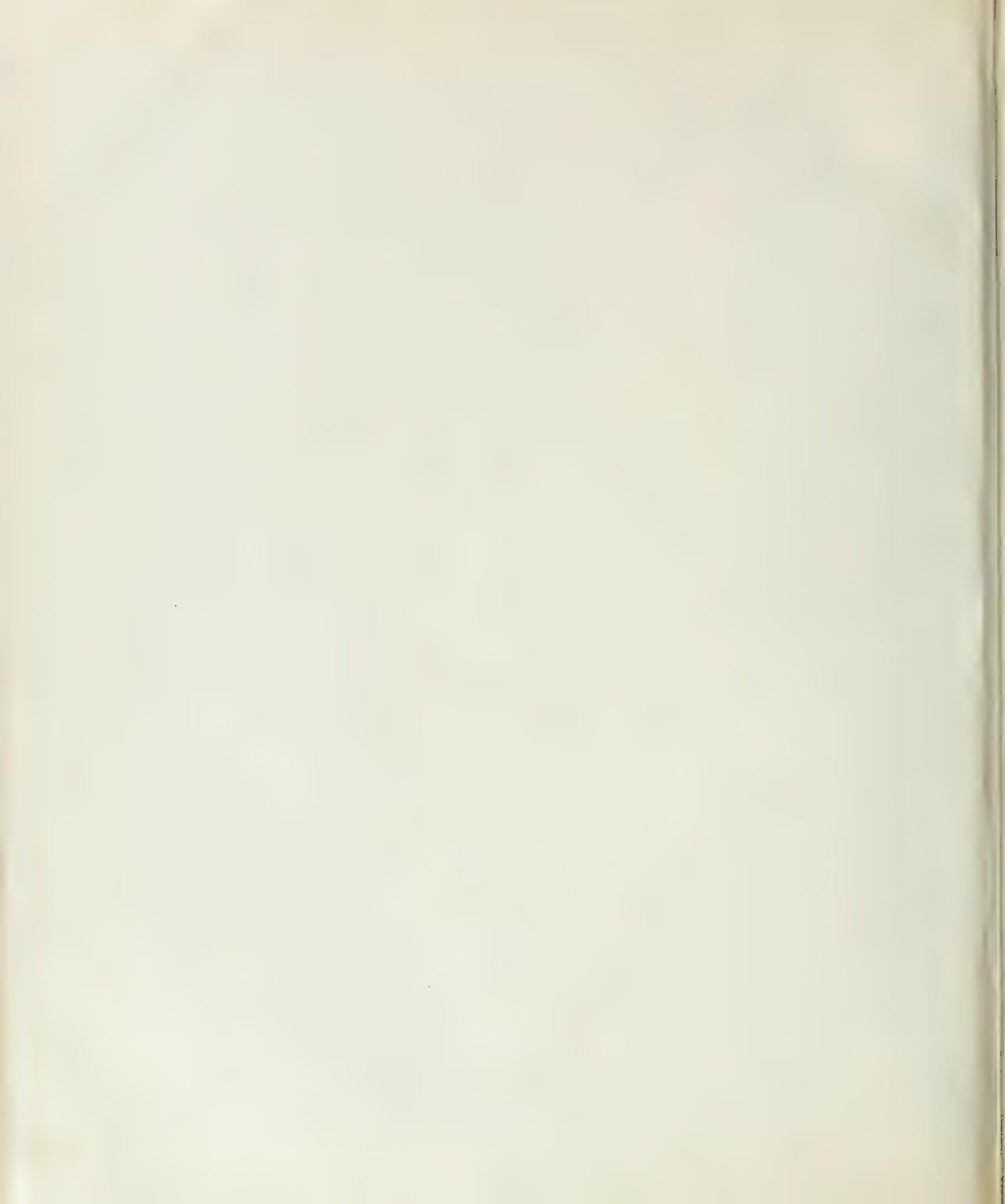


FIG. 2.—Electrocardiogram (Second Lead). The signals are not reproduced in this print, but the first mark indicates the signal to accelerate, the second indicates the signal to retard.



# THE INNERVATION OF THE TENSOR VELI PALATINI AND LEVATOR VELI PALATINI MUSCLES

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Gowers began his discussion of the nerve supply of the tensor veli palatini and levator veli palatini muscles with the remark that "the origin of the nerve supply to the palate is one of the most obscure questions connected with the anatomy of the cranial nerves."<sup>1</sup> During a recent study of the physiological relation of the palatal muscles to the Eustachian tube, a review of the literature concerned with the innervation of those muscles disclosed so great a variety of conflicting opinions, clinical observations and experiments that, at the suggestion of Dr. W. H. Howell, it was decided to attempt to study the matter experimentally, since a method had been perfected by means of which the muscles of the palate could easily be exposed, with their nerve supplies intact, for observation in the living animal. It was believed that such a direct method of study would obviate certain difficulties of interpretation which must have hampered many experimenters and clinical observers in their attempts to recognize the movements of the individual muscles while they remained hidden by the mucous membrane of the palate.

The brief outline of the conclusions of previous workers represents an arbitrary selection and by no means exhausts the entire literature reviewed.

## 1. THE MOTOR SUPPLY OF THE TENSOR VELI PALATINI MUSCLE

The anatomical relationship between the tensor veli palatini muscle, the otic ganglion and the fifth nerve has long been described, and these descriptions, rather than definite experimental evidence, have led the majority of writers to place the motor supply of this muscle in the fifth nerve; for clinical and experimental studies have yielded neither uniform nor satisfying results.

In 1842, Longet<sup>2</sup> described slight movements of the soft palate when he stimulated, in animals, the motor root of the fifth nerve. He assumed that these movements were produced by contractions of the tensor veli palatini, and he therefore placed the motor supply of this muscle in the fifth nerve. Debrou<sup>3</sup> could not detect the slightest palatal movement on stimulation of the fifth nerve, and wrote that "the fifth nerve has nothing whatever to do with the movements of the soft palate." However, he accepted the opinion that the tensor veli palatini is innervated by the trigeminal, and assumed in consequence that the muscle must have very little effect upon the soft palate. Reid<sup>4</sup> had the same experience and wrote, as a result of his experiments on the palatal muscles, that the vagus "is the principal if not the sole motor nerve of these parts"; but he mentioned the fact that a twig from the external pterygoid branch of the fifth nerve to the tensor veli palatini muscle had been described, and he did not exclude the

possibility that this nerve might contribute to the motor supply of the tensor. Hein, in 1844, wrote that he had torn away the mucous membrane in freshly decapitated animals and had been able to see contractions of the belly of the tensor veli palatini muscle when he stimulated the motor root of the fifth nerve.<sup>5</sup> The anatomical situation of this muscle makes it difficult to understand how its contractions could be seen with no further dissection than the removal of the palatal mucous membrane.

In 1861, Politzer<sup>6</sup> stimulated the motor root of the fifth nerve within the cranial cavity and observed a dilatation of the pharyngeal orifice of the Eustachian tube on the same side. From anatomical studies he had become convinced that the tensor veli palatini functions as a dilator muscle of the Eustachian tube, and he therefore concluded that this muscle is innervated by the fifth nerve. Turner,<sup>7</sup> on the other hand, vigorously rejected the fifth nerve as the motor supply of the tensor veli palatini and wrote: "I have been unable to find a single recorded case in which disease of this nerve (fifth) was associated with paralysis of the tensor palati muscle, which theoretically would be shown by a dragging of the raphé to the non-paralyzed side. Sir Charles Bell, who records many cases of disease of this nerve, does not mention the condition of the palate in any of them. Romberg never saw paralysis of the tensor palati associated with disease of the motor division of fifth nerve; and Dr. Gowers holds the same opinion. Experimental evidence also is not of a satisfactory nature. John Reid failed to elicit palatal movements on irrigating the motor division of the trigeminal nerve; and Longet does not mention any effect on the palate when this nerve was stimulated."<sup>8</sup> Turner placed the motor supply of the tensor veli palatini in the eleventh nerve by way of the otic ganglion. His reasons are entirely theoretical.

In 1862, Chauveau's experiments<sup>9</sup> led him to place the innervation of all of the palatal muscles in the tenth nerve. Rethi,<sup>10</sup> in 1893, wrote that he had torn away the palatal mucous membrane and had observed movements of the tendon of the tensor veli palatini when he stimulated the trigeminal nerve. Vulpius's experiments,<sup>11</sup> however, brought him to the conclusion that the fifth nerve does not supply any of the palatal

\* It has already been stated that Reid did not deny the possibility of the relation of the fifth nerve to the tensor veli palatini muscle; and in justice to Longet it should be noted that if one turns to the reference cited by Turner (*Anat. et Phys. du Système Nerveux*, t. 2, Paris, 1842) it will be found that Longet writes: "La portion non-ganglionnaire ou petite racine du trijumeau, galvanisée dans le crâne, détermine des secousses très manifestes dans la mâchoire inférieure, en même temps qu'elle imprime de légers mouvements au voile palais. C'est elle, en effet, qui préside aux mouvements d'élevation, d'abaissement, de diduction de la mâchoire inférieure, ainsi qu'à la tension du voile palatin." (Italics mine. A. R. R.)

muscles. He placed the motor supply of the palate in the tenth and eleventh nerves, and his experiments suggested the possibility of the ninth as well. In 1905, Cushing<sup>12</sup> described his observations made upon patients in whom the motor root of the trigeminal nerve had been cut during extirpation of the Gasserian ganglion. In one case he stimulated electrically the mandibular nerve at operation and saw movements of the soft palate occur during the stimulation. In four cases, out of a series of twenty, he observed changes in the appearance of the palatal curtain develop after operation, and he attributed these changes to a paralysis of the tensor veli palatini muscle following destruction of the fifth nerve. In the same year, Tissier<sup>13</sup> wrote that the tensor veli palatini is innervated by the seventh nerve.

More recently, Vernet<sup>14</sup> has concluded from an examination of the literature that the fifth nerve must supply the tensor veli palatini muscle; while Davies' studies on the trigeminal nerve<sup>15</sup> led him to write that "the balance of evidence seems to show that the fifth nerve has nothing whatever to do with the nerve supply of the palatal muscles." Among contemporary editions of standard text-books of anatomy we find that Cunningham<sup>16</sup> gives the fifth nerve as the innervation of the tensor veli palatini, while Gray<sup>17</sup> states that the muscle is supplied by a twig from the otic ganglion, and refers to Turner's article which suggests the eleventh nerve as the origin of the ganglionic twig.

#### EXPERIMENTS

A careful study of the literature made it evident that perhaps the greatest source of error in the attempts to determine the nerve supply of the individual palatal muscles lay in the fact that, almost without exception, previous experimenters and clinical observers have not been able to see the muscles which they were studying. The intact soft palate is watched while a nerve is stimulated; if the palate moves, the nerve is assumed to supply one or more of the palatal muscles; which muscle or muscles it is credited with innervating depends, in each case, upon the imagination of the observer who is attempting to identify the movements of the individual muscles while they lie hidden behind the palatal mucous membrane. Indeed, Hein and Rethi, as far as I have been able to discover, are the only writers who have reported experiments in which the palatal mucous membrane was removed. Hein speaks of stripping the mucous membrane from the belly of the tensor veli palatini muscle in freshly killed animals in order to watch the effect upon the muscle of nerve stimulation; by which he must have meant the nasopharyngeal mucous membrane which he exposed by splitting the head sagittally, since the mere removal of the palatal mucous membrane will not bring the muscle into view. Rethi speaks only of exposing the tendon of the tensor veli palatini, which is not an entirely conclusive experiment, for the reason that the tendon of this muscle fans out into a fascial layer of the soft palate which is closely related to the palatopharyngeus, the pterygo-pharyngeus and the internal pterygoid muscles as well. The reason why more direct experiments have not been made lies,

apparently, in the difficulties encountered in the attempt to expose the palatal muscles in the living animal by dissection, since the irritability of muscle and nerve hardly persists long enough after death to permit a careful dissection of the region and subsequent satisfactory observations. The chief difficulty of the operation seems to have been uncontrollable hemorrhage. Thus, Willems<sup>18</sup> in 1911, after unsuccessful attempts to expose the palatal muscles in living animals in order to study the origin of their motor fibres, wrote: "La moindre incision de la muqueuse est suivie d'une hémorragie veineuse telle que le champs opératoire en est complètement masqué et que l'animal y succombe en quelques seconds." Such hemorrhage can, however, be controlled perfectly by hemostats and appropriate ligatures, so that the entire operation can be performed with a negligible loss of blood.

The anatomical and physiological relations of the palatal muscles of the dog resemble strikingly those of man; furthermore, the great majority of previous workers have made this animal the subject of their experiments. Dogs were therefore used in all of the present observations. The procedure by which the palatal muscles were exposed with their nerve supplies intact is here quoted from a previous paper:<sup>19</sup>

A dog is anesthetized, tracheotomy performed and connection established with an ether-respiration bottle by means of a tracheal cannula. Both common carotid arteries are ligated to minimize hemorrhage, as it is desirable to introduce about the delicate palatal muscles as few ligatures as possible. The immediate collateral circulation is ample to maintain satisfactorily the nutrition of the structures during the experiment. A mouth-gag is introduced to hold the jaws widely separated, and the tongue is drawn forward and stitched to the lower lip. The hamular processes of the pterygoid bones can be felt on either side as distinct bony prominences in the roof of the mouth. Using these as landmarks, an incision is made through the mucous membrane of the soft palate from a point about one centimeter anterior to them, extending backward in the midline almost to the insertions of the levator veli palatini muscles in the uvular region. Dissection is carried lateralward along the plane of the fibrous layer of the soft palate formed by the tendinous expansions of the tensor veli palatini muscles. The hamular process of the pterygoid bone is exposed, and the palatopharyngeus muscle is seen stretching from this point backward toward the pharynx.\* Careful separation of the fibers of this muscle from those of the closely associated pterygopharyngeus reveals the levator veli palatini, which passes between them on its way to the soft palate, forming with them an angle of about 70°. The dissection is continued across the hamular process, and the internal pterygoid muscle is seen just lateral to this landmark, extending anteriorly along the palatine bone. This muscle completely hides the tensor veli palatini in such an approach. It is necessary, therefore, to remove the overlying fibers of the internal pterygoid in order to expose the tensor veli palatini, which can then be seen as a rather pale, very small muscle, the fibers of which extend from the pterygoid hamulus lateralward, backward and upward toward the inferior portion of the temporal bone. The integrity of the nerve supply was, in all cases, tested after completing the dissection by watching for the contraction of the individual muscles during the execution of the swallowing reflex, in which they both normally participate.

\* At this point, ligation of the lateral palatine vessels greatly reduces the liability of hemorrhage.

Having exposed the tensor and levator veli palatini muscles with their nerve supplies intact, the region is covered with gauze soaked in warm saline. The skull is then trephined and quickly cut away until the brain and medulla are exposed. No attempt is made at this point to arrest hemorrhage, as the animal is immediately decapitated and the brain removed as speedily as possible after cutting the roots of the cranial nerves close to their points of emergence from the brain. The various nerves are then stimulated electrically within the cranial cavity, and the effects of such stimuli are observed by watching the behavior of the naked tensor and levator veli palatini muscles during the stimulation. The irritability of muscle and nerve persists in such a preparation long enough to permit satisfactory observations to be made. For trustworthy results in such experiments, it is necessary to destroy the dural connections between the various nerves, carefully to dry the area about the nerve to be stimulated, and to use a moderate or weak current, preferable with unipolar electrodes. Bipolar electrodes, a strong current and dural or moisture connections between the nerves will, obviously, be productive of unreliable observations because of the diffusion of the current to nerves other than those to which the electrodes are actually applied. It seems certain that some of the incompatible results reported in the literature must have arisen from a neglect of these precautions.

In every experiment, stimulation of the mandibular branch of the fifth nerve caused definite, vigorous contractions of the tensor veli palatini muscle on the side stimulated. The maxillary and ophthalmic divisions of the fifth, and all of the remaining cranial nerves were carefully stimulated in a large number of experiments with no effect whatever upon this muscle. The tensor veli palatini clearly derives its motor supply from the mandibular division of the fifth nerve.

Twigs from the otic ganglion to the tensor veli palatini muscle are commonly described. With the idea of trying to determine its rôle, several attempts were made to paralyze the ganglion. The foramen ovale was enlarged by chipping away the bone about it and the otic ganglion was exposed. The mandibular nerve was stimulated, and contractions of the tensor veli palatini were observed. Then the ganglion was painted with nicotine, and the mandibular nerve was again stimulated. It will be remembered that in all of these experiments fatigue and progressive loss of irritability of muscle and nerve are important factors in the interpretation of observations; but comparison between the experiments in which nicotine was applied and those in which there was no such treatment of the otic ganglion shows no appreciable difference in the time required for loss of response of the muscle to stimulation of the nerve. While this point would bear further investigation, the fact that stimulation of the remaining cranial nerves fails to cause contraction of the tensor veli palatini makes it certain that the muscle does not receive motor fibres by way of the otic ganglion or by any other route from any cranial nerve other than the fifth.

One of the chief objections to the view that the fifth nerve supplies the tensor veli palatini has always been the fact that

paralysis of the palate is rarely observed clinically in cases of disease of this nerve. To begin with, it is difficult to understand how one could expect to detect a paralysis of the tensor veli palatini by inspection of the buccal surface of the palate. None of the fibres of this muscle lie in the palate and therefore wasting of the muscle cannot be detected by oral inspection. As for the "theoretical dragging of the raphé to the non-paralyzed side,"<sup>7</sup> this, even if it could occur, would be present only during contraction of the non-paralyzed muscle, and it is to be remembered that the tensor contracts only during certain reflexes (deglutition; yawning; sneezing) and that normally it remains at rest during ordinary elevation of the palate produced by forced respiration or by vowel enunciation.<sup>18</sup> Oral inspection of the palate during swallowing is practically impossible in an unanesthetized patient; and I have found no record of examination of the palate during the yawning reflex in cases of fifth nerve disease. So the fact that palate paralysis has not regularly been observed, does not appear to be a valid objection to the idea that the tensor veli palatini was involved in these cases. But aside from this consideration, a careful study of the action of the tensor veli palatini muscle, with the idea of determining to what extent its contraction influences the condition of the palate, has led to the conclusion that it would be very difficult under any circumstances to detect paralysis of this muscle by inspection of the intact soft palate. Using anesthetized animals, the normal appearance of the palate was observed during deglutition, in which reflex the tensor veli palatini muscles participate. Then, through a small, lateral incision in the mucous membrane just over the hamular process, the tendon of the tensor veli palatini on one side was exposed and cut through. The swallowing reflex was then set in motion again while the soft palate was observed. Although the raphé was marked with India ink in order to be able more easily to detect its movements, there was seen not the slightest dragging of the mid-line of the palate to the non-paralyzed side. The palate was perfectly symmetrical while at rest, and during deglutition the paralyzed side did not present an appearance different in any respect from that of the normal side. After such experiments, a dissection has always been made to make certain that the tendon of the tensor had been entirely severed; and it was further determined that the muscle on the normal side had been functioning properly by watching its contraction during deglutition after it had been exposed by dissection.

If the anatomical structure of the soft palate be studied, it will be found that, after winding around the hamular processes, the tendons of the tensor veli palatini muscles fan out in a fibrous sheet which underlies the nasopharyngeal mucous membrane of the palate. This fibrous sheet has a definite stiffness even when the tensor muscles are at rest; a fact which can be determined by cleanly exposing this layer of the soft palate in an anesthetized animal. If now the tensor veli palatini of one side be stimulated, there will be seen not the slightest deflection of the midline of the sheet toward the side stimulated, even during the most vigorous contractions of the muscle. The tendon will be seen gliding over the hamu-

lar process, but pulling in a direction that proceeds from the margin of the hard palate. It has been pointed out by Henle that the tensor veli palatini is inserted chiefly into the fibrous prolongation of the hard palate, and that its tendinous expansion dwindles away toward the posterior, free end of the soft palate, so that contraction of the muscle cannot affect the soft palate very much. Indeed, Allen wrote in 1883, that at that date it was no longer believed that the tensor veli palatini can actually make the soft palate tense.<sup>19</sup> Debrou<sup>2</sup> and others have recognized this; and one needs no clearer evidence of the difficulty of determining unilateral contraction of the muscle by oral inspection than that afforded by the majority of experimenters who have been unable to see palatal movement on stimulation of the fifth nerve, although the tensor veli palatini was contracting, as the present experiments have shown. Cushing's single case,<sup>20</sup> the experiments of Longet,<sup>2</sup> and two isolated experiments in Hein's series<sup>5</sup> are the only instances which I have found in the literature in which movements of the intact soft palate have been seen on stimulation of the fifth nerve; and it will be remembered that Longet described no dragging of the raphé toward the side stimulated, but only "légers mouvements du voile du palais,"<sup>2</sup> while both of Hein's cases were so inconclusive that he resorted to other means in the attempt to establish the relation of the fifth nerve to the palatal muscles. Certainly, contraction of the muscle does stiffen the anterior portion of the soft palate to some degree; but the present experiments indicate that paralysis of the muscle can rarely, if ever, be detected by inspection of the intact soft palate, and then, perhaps, only in cases of unusual development or anomalous insertion of its tendon.

During the progress of these experiments, there was a patient under observation in The Johns Hopkins Hospital who had a parasyphilitic unilateral paralysis in the domain of the third, fifth and seventh cranial nerves. There was a bilateral involvement of the sixth nerve. The remaining nerves were unaffected. There was no palate paralysis, but nasopharyngoscopic examination showed that the pharyngeal orifice of the Eustachian tube on the affected side remained quite stationary during deglutition, offering in appearance a striking contrast to the normal reflex opening of the orifice on the unaffected side. Since it has been shown that the tensor veli palatini is the only muscle which can open the Eustachian tube,<sup>21</sup> this condition was apparently produced by a paralysis of this muscle following disease of the fifth nerve. Such a paralysis of the tensor supports Cushing's suggestion<sup>22</sup> that the aural disturbances occurring after operative destruction of the motor root of the fifth nerve may result from the inability of the Eustachian tube to function properly. It remains for further observation to determine whether such a visually distinct paralysis of the Eustachian tube will be found to be a constant accompaniment of paralysis of the tensor veli palatini muscle.

## 2. THE MOTOR SUPPLY OF THE LEVATOR VELI PALATINI MUSCLE

In 1841, Debrou<sup>2</sup> stimulated electrically the various cranial nerves of dogs while observing the effect upon the soft palate,

and concluded that the levator veli palatini is supplied by the ninth nerve. Longet's experiments of a similar nature<sup>23</sup> led him to place the motor supply of the levator in the seventh nerve, and the influence of his opinion can be traced through a great mass of clinical and experimental literature concerned with this question. Hein,<sup>6</sup> however, in 1844, wrote that stimulation of the seventh and ninth nerves had no effect whatever upon the soft palate, but that stimulation of either the tenth or the eleventh nerve caused vigorous contractions of the levator veli palatini muscle. Reid<sup>4</sup> wrote, on the basis of his experiments, that the vagus is the principal, if not the sole, motor nerve of the palate. In 1886, Vulpian's experiments<sup>24</sup> led him to the conclusion that the levator veli palatini is supplied by the tenth and eleventh nerves, and perhaps by the ninth as well. Horsley and Beevor,<sup>25</sup> in 1888, described their experiments which led them to place the motor supply of the levator veli palatini in the eleventh nerve. In 1893, Rethi's experiments indicated that the levator is supplied by the tenth nerve. Geronzi,<sup>26</sup> in 1906, added the twelfth to the list of nerves described as innervating this muscle, while Willems,<sup>27</sup> in 1911, wrote that the levator is supplied by the fifth nerve. In 1918, Vernet<sup>28</sup> concluded from an examination of the literature that the evidence seemed to be in favor of the eleventh nerve as the motor supply of the levator veli palatini.

Wolffert<sup>29</sup> pictured his dissections which led him to believe that the levator veli palatini is supplied by a branch formed by the union of fibers from the ninth and tenth nerves, and wrote: "Comparantibus nobis ea, quae in diversis operibus anatomicis et physiologicis de illo musculo ejusque nervis tradita sunt, mirum videbitur, quanta varietas sententiarum de illa re exstet"; and indeed, reference to standard, present-day texts will still arouse in us some wonder, for the nerve supply of the levator veli palatini will be found to be variously given as the tenth nerve;<sup>22, 23</sup> the seventh nerve;<sup>24, 25</sup> the eleventh nerve;<sup>26, 27, 28</sup> and finally, the superior maxillary branch of the fifth.<sup>29</sup>

## EXPERIMENTS

After exposure of the levator veli palatini muscle with its nerve supply intact, in the anesthetized animal, all of the cranial nerves were carefully stimulated within the skull in the manner which has been described above, while the naked muscle was kept under observation. It was at once found that it was impossible to produce contractions of the muscle by stimulation of any cranial nerve other than the ninth, tenth or eleventh. At first, the confusing observation was made that contractions of the muscle would follow stimulation of either of these nerves, although the ninth would cause contractions only occasionally. These three nerves make their exit from the cranial cavity through the same foramen, and as they pass through the foramen they are bound together within the same dural sheath. It is evident, then, that radiation of the current can easily occur when either of the nerves is stimulated. Weak currents were therefore used in a large number of experiments, and it was found that, in all cases, the levator veli palatini would respond to stimulation of the eleventh

nerve; an occasional, inconstant response has followed stimulation of the vagus rootlets, while stimulation of the ninth nerve was entirely without effect.

More definite evidence that the accessory nerve supplies the levator veli palatini was obtained by studying the effect of section of the roots of this nerve in the living animal. In these experiments, after the usual palatal dissection and the determination of the integrity of the nerve supply of both levator muscles, the atlas, the atlanto-occipital membrane and the occipital bone are laid bare by dissection. Following a suggestion of Claude Bernard,<sup>20</sup> a small hole is trephined immediately under the occipital protuberance and a concentrated solution of iron persulphate is injected into the sinus after preliminary ligature of the jugular veins. This procedure coagulates the blood within the sinus, and is a distinct aid in combating the hemorrhage which occurs when the sinus is cut through. The atlanto-occipital membrane is then incised, the dura is entered, and the lower portion of the occipital bone is cut away with rongeurs until the medullary roots of the ninth, tenth and eleventh nerves can be clearly exposed by gently retracting the overhanging cerebellum. Bleeding from the cut surface of the bone is controlled with wax, and great care is taken to try to prevent unnecessary hemorrhage from the small vessels along the cerebellum and medulla, for such bleeding, while unimportant as regards the survival of the animal, tends to collect about and entirely obscure the rootlets of the vago-accessory complex. Having obtained a good exposure of the rootlets of the ninth, tenth and eleventh nerves, the spinal portion of the eleventh on the right side was cut just below the point where it joins the bulbar rootlets. The swallowing reflex was then set in motion, and the levator veli palatini muscles were seen to contract normally on both sides. Then the bulbar rootlets of the eleventh nerve were cut on the right side, after which it was seen that during deglutition, while the levator on the left side contracted vigorously, the muscle on the right side remained motionless. Such an experiment performed upon an animal in whom the soft palate had been left intact produced, during deglutition, the characteristic asymmetry of the palatal curtain which is observed clinically in cases of paralysis of the levator veli palatini muscle. A careful autopsy was performed after every experiment in order to make certain that the rootlets of the ninth and tenth nerves had not been damaged. The evidence obtained from the stimulation experiments, combined with the results following nerve section, lead us to the conclusion that the levator veli palatini muscle receives its motor supply from the bulbar portion of the eleventh nerve.

It is not necessary to assume that experimental error lay at the bottom of the results of the several observers who have concluded that the lower rootlets of the vagus may carry fibres destined for the levator veli palatini. The work of Van Gehuchten,<sup>21</sup> Chase and Ranson<sup>22</sup> and of others has demonstrated that the so-called bulbar portion of the eleventh nerve is, in reality, a part of the vagus, and is entirely distinct, both in origin and distribution, from the spinal portion of the eleventh nerve. In the current edition of Piersol's Anatomy it

is stated that "it is generally admitted that the bulbar or accessory portion of the eleventh nerve forms an integral part of the motor division of the vagus and hence should be included with the efferent fibres of the tenth."<sup>23</sup> These facts make it clear that any attempt sharply to limit the functions of the various rootlets must be artificial; and it is possible that in some cases fibres to the levator palati may pass through the lower rootlets of what is commonly regarded as the vagus proper. However, the so-called bulbar rootlets of the eleventh undoubtedly constitute the main route for the motor fibres to this muscle, and I have no evidence that any of the fibres so destined pass through the so-called vagus proper. Even Vulpian, who believed that the inferior rootlets of the tenth (those immediately adjoining the bulbar rootlets of the eleventh) carry motor fibres for the palate, wrote: "Peut-être ces divers filets radiculaires appartiennent-ils tous aux nerfs spinaux ou accessoires de Willis."

#### SUMMARY

The tensor veli palatini and levator veli palatini muscles have been exposed, with their nerve supplies intact, by dissection in the living animal, and the various cranial nerves have been stimulated within the skull while the naked muscles were observed; and it was determined that:

1. The fifth nerve is the only cranial nerve which supplies motor fibres to the tensor veli palatini muscle. The failure of most clinical observers to detect paralysis of the palate in cases of disease of the fifth nerve arises from the fact that the tensor veli palatini exerts, ordinarily, no effect upon the soft palate that can be detected by oral examination.
2. The method of intracranial stimulation, combined with experimental paralysis of the muscle produced by nerve section, places the motor supply of the levator veli palatini muscle in the so-called bulbar portion of the eleventh nerve (more properly speaking, in the inferior rootlets of the tenth nerve, since the bulbar portion of the eleventh has been shown to be, in reality, an integral part of the vagus).

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## ANAPHYLAXIS\*

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In my first lecture I dealt with the experiments which led us to an explanation of the paradoxical depressor action on the circulation of histamine and similarly acting substances, which are characteristically stimulants of plain muscle. I indicated that this anomalous vasodilator action, which we had been led to regard as an action on the tone of the capillaries, was seen only in certain species, such as the carnivora and the monkey, and showed how, when intensified and prolonged, it led to a shock-like circulatory depletion. Although our attention was confined to the effect on the circulation, there was already perceptible, then, a well-marked divergence between the phenomena seen in different species. This divergence becomes more pronounced when the effects on other organs are brought into the picture, as in studying the general symptoms of poisoning produced by large doses. We have seen already that in the anaesthetized cat such larger doses produce a circulatory shock. In the dog a very similar complex is produced under like conditions. It differs in some details from that seen in the cat. Thus in the dog the preliminary steep fall and secondary rise of blood-pressure are not seen; the arterial pressure falls from the first with the accompaniment of a violent dyspnoea, until it attains a shock-level of some 30 mm. of mercury. The concentration of the arterial blood is quite pronounced, but usually less so than in the cat. The effect in the dog's capillaries seems also to be less generally diffused, those of the liver being more conspicuously affected than others, so that this organ swells and becomes somewhat tense with blood. This is in accordance with the conspicuous liability of the liver capillaries of the dog to the action of poisons of this type, as shown in the experiments of Starling, Thompson, Edmunds and others. On the whole, however, the symptoms in the cat and dog have the same general aspect. In both species hypodermic injection even of large doses produces a prolonged narcosis and lethargy, but is

seldom fatal. In the guinea-pig, if histamine is injected into a vein without an anaesthetic, the result is remarkably different. The hair becomes erected, especially on the head, the animal gives a chattering cough, makes violent inspiratory efforts accompanied by convulsive movements of all the limbs, often leaps from the table, falls on its side, and with a few terminal inspiratory spasms is dead. If the chest is opened immediately after death, the heart is found to be beating, while the lungs are fixed in extreme distension, and cannot be made to collapse even by external pressure. A dose of 0.5 mgm. of histamine suffices to kill a large guinea-pig in this manner. If injection be made intraperitoneally much larger doses fail to kill, and the condition produced is that of a prolonged collapse, with pronounced respiratory embarrassment; recovery may take place even after hours. During the collapse a conspicuous feature of the condition is the rapid fall of body temperature. We have observed a fall in the rectal temperature from 38° to 28° C. in an hour, with subsequent recovery, after intraperitoneal injection of 3 mgm. of histamine.

In the rabbit, again, with hypodermic or intraperitoneal injection comparatively large doses are tolerated, with the narcotic effect which seems common to all species. Intravenously, much smaller doses cause rapid death with convulsions, the actual cause of death being, in this case, an acute failure of the right chambers of the heart, the respiratory center continuing to act for a brief period after the heart has stopped. This acutely fatal effect in the rabbit, though its mechanism is different, resembles the asphyxial death in the guinea-pig in being prevented or modified by deep anaesthesia. If the rabbit is deeply under urethane this fatal effect on the heart does not appear; under such conditions, as I have mentioned earlier, histamine produces a simple rise of the arterial pressure.

These effects in the different species, superficially so dissimilar, are not difficult to understand in the light of the analysis of the effects of histamine, with which I dealt in my last lecture. You will remember that its different effects could

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be interpreted as due to its contrasted actions on plain muscle and on the walls of the capillaries, the former being stimulated to tonus, while the normal tone of the latter is weakened or abolished. In the carnivora this effect on the capillaries, leading to peripheral accumulation of blood and depletion of the heart, is the predominant factor in the effect; and not only is it not suppressed, it is even intensified by prolonged anaesthesia with anaesthetics of the alcohol series. In the guinea-pig and the rabbit the effect on plain muscle comes into the foreground. In the guinea-pig the plain muscular coats of the bronchioles are so richly developed and reactive, the tubes are so small and their lining mucous membrane so thick and folded, that, as Schultz and Jordan have shown, there is easily produced a valve-like obstruction of the air-way, leading to asphyxia, with extreme, fixed distension of the lungs. In the rabbit the failure of the right side of the heart seems to be due mainly to intense constriction of the branches of the pulmonary artery, causing the right chambers of the heart to become overdistended, so that they pass into a fatal fibrillation. Probably the effect is accentuated by some measure of bronchial constriction, but this is not, as in the guinea-pig, the predominant factor in the result. Deep anaesthesia with ether or urethane greatly weakens in both species these plain muscle effects, whether on the bronchi or on the pulmonary arteries.

I have devoted more time to the analysis of these effects, with their curious appearance of contrast in various species, than the subject would probably deserve, if we were concerned merely with the action of histamine as a pharmacological curiosity. Their real interest appears when we find the same types of action, with the same contrasts between the different species, appearing not only in the reaction of the different animals to a large class of protein poisons, but also in the reaction of the same types, when specifically sensitized, to normally inert proteins, in the so-called anaphylactic shock. No one familiar with the anaphylactic shock, as seen in different species, can fail to be struck with the extraordinary similarity. Here, again, the conspicuous feature of the effect in the anaesthetized dog is the profound collapse of the systemic arterial pressure, as Biedl and Kraus, Manwaring, Pearce and Eisenbrey, among others, have shown. Here, too, in the guinea-pig, especially when the sensitizing protein is reinjected intravenously, the picture is dominated by an intense bronchial spasm, as first shown by Auer and Lewis, producing an asphyxiation so rapidly and dramatically fatal that other effects usually have not time for development. In the rabbit, again, the main feature of the anaphylactic shock is heart-failure, as Auer demonstrated.

In some respects the anaphylactic shock differs from that produced by histamine, and resembles more closely that produced by more complex proteinogenous poisons, such as Witte's peptone. For example, the loss of the normal property of coagulation of the blood, especially in the dog, is characteristic of the anaphylactic shock, and of the action of Witte's peptone, but not of that of histamine. In the dog, too, the concentration of the capillary poisoning on the vessels of the liver is more conspicuous in the anaphylactic shock and in

the action of peptone than in that of histamine. Manwaring showed, indeed, that in the dog exclusion of the liver from the circulation wholly, or almost wholly, abolished the circulatory features of the anaphylactic reaction. This was confirmed by Voegtlind and by Bernheim, by a more elegant method. In the rabbit, heart failure again seems to be a common feature in the different actions. Till recently it appeared doubtful whether the mechanism of its causation in the anaphylactic shock is identical with that which I have described in the case of histamine. Auer attributed the failure of the rabbit's heart in anaphylactic shock to a poisoning of the heart muscle; but quite recently Coca has reinvestigated the effect, and has demonstrated the predominant share in its production of an intense constriction of the pulmonary arterioles. The resemblance to the effect of histamine is, therefore, established in this case also. It is evident that we may safely regard the anaphylactic symptoms in the dog, the guinea-pig and the rabbit—in which species they have most thoroughly been studied, as due to a complex of contraction of plain muscle and loss of capillary tone closely resembling that produced by histamine; and the appearance of this syndrome again in the reaction of a specifically sensitized animal to a normally inactive protein gives abundant food for reflexion. The similarity is so striking that it is impossible to avoid the suggestion of a community of cause, leading to a community of effect. It is to a consideration of the meaning of this correspondence that I wish to devote the greater part of this lecture.

We must, in the first place, review as rapidly as possible what is known as to the nature of the anaphylactic condition, and of the events which lead to the appearance of the symptoms known as the anaphylactic shock. Knowledge has already moved far from the position in which anaphylaxis was regarded as the opposite of immunity. You will remember that, when Richet first clearly recognized the condition, the accidental circumstances of his experiments gave the phenomenon this appearance of a mere accentuation of sensitiveness to certain protein poisons. He happened to be working with poisonous proteins from sea-anemones, from edible mussels and from a poisonous plant—*Hura crepitans*. These proteins had of themselves, on a normal dog, a poisonous action of the general type which we have been discussing. When a dog, which had received a sub-toxic injection of one of them, was given a second injection of the same poison some weeks later, it responded with a violent, immediate and often fatal reaction, which was easily mistaken for a response of the kind given by a normal dog to a large dose, but accelerated in its onset and aggravated in its severity. Richet supposed that he had found the converse or antithesis of immunity, and the legacy from that mistake is the name "anaphylaxis." This has nothing to be said in its favor from the point of etymology; it gives faulty expression to a mistaken conception; but usage has established it firmly.

The true nature of the phenomenon soon became apparent. Arthur demonstrated the increasingly poisonous action on the rabbit of a second and subsequent injections of a substance normally so innocuous as horse serum. It was made clear that

the symptoms resulting from the second injection of a protein, when this followed the first injection at a suitable interval, had no connection with the normal toxicity of the substance. An animal, indeed, might be and often was at the same time immune to the normal toxic action of a protein, and anaphylactic to it simply as protein. Anaphylaxis was a condition in which the animal reacted to a normally harmless substance as to an acute poison.

The recognition by Theobald Smith and others in this country of the extreme sensitiveness to horse-serum, shown by guinea-pigs which had survived a standardizing test for anti-toxin, constituted practically a rediscovery of anaphylaxis in another species, and gave an immense impetus to its investigation. Thenceforward, the special characteristics of the guinea-pig have made it the chosen subject of a large proportion of the experiments dealing with the phenomenon. The ease and regularity with which animals of this species can be sensitized, the minuteness of the dose which suffices for their sensitization, and the rapidly lethal character of their response to reinjection, have greatly impressed the imagination of investigators, and have given almost a sensational interest to the phenomena.

There has been a perceptible danger, in some quarters, lest the somewhat dramatic symptom-complex shown by the guinea-pig might be itself regarded as characteristic of the anaphylactic reaction. It is necessary to keep clearly in view that the characteristic of the anaphylactic condition is not the nature of the symptoms, which a large number of protein poisons evoke, but their appearance in response to the injection of a substance which normally has not this action, owing to a specific sensitiveness conferred by a previous injection. Bearing this in mind, and also being careful not to generalize too hastily from results obtained only on the guinea-pig, we may consider the evidence as to the nature of anaphylaxis, obtained chiefly by experiments on that species.

The main features of the condition were soon made clear. A minimum interval of 6 to 10 days, according to the size of the dose and the method of giving the reinjection, must elapse before the abnormal sensitiveness could be detected. It then rapidly attained a maximum development, and in the guinea-pig it lasted for the rest of the natural life of the individual. The specific sensitiveness could be transferred to a normal guinea-pig by injection of blood or serum from a guinea-pig, or other animal, which had been rendered anaphylactic; so that there was a "passive" anaphylaxis, corresponding to a "passive" immunity, and indicating that anaphylaxis, like immunity, depends on the presence of a specific antibody of some kind. But there is one curious feature in the production of this passive anaphylaxis in the guinea-pig, which is too frequently left out of account in discussing the nature of the condition. The passive anaphylaxis does not appear immediately, even if the anaphylactic serum is injected intravenously. The first traces of sensitiveness appear only after the lapse of some 5 or 6 hours, and the condition is not fully developed for 24 hours. While, therefore, everything points to the dependence of the anaphylactic condition on the presence of a specific antibody, which can be transferred from one

animal to another, the mere presence of this antibody in the blood is not sufficient to produce the condition. Time must be allowed for its development, and we are driven to suppose that the antibody must acquire some special relation to the constituents of the body fluids or the tissues, before it can become effective in rendering the animal anaphylactic.

The anaphylactic state appeared to be so unlike those usually associated with the presence of antibodies, that it was at first naturally supposed that the anaphylactic antibody was of a special type. It must still be recognized as possible that it may be so. On the other hand, there is a great deal of evidence which points in the direction of its identity with the so-called "precipitin"; that is to say, with an antibody having this property, that, when it is mixed with the antigen, the two undergo a mutual aggregation of their colloidal particles.

The evidence for this identity is mostly indirect, but none the less highly suggestive. The type of substance which is preeminently effective in producing anaphylaxis is that which characteristically causes precipitin formation, namely, that of the large-moleculed native proteins. Modifications which destroy the power of evoking formation of precipitins, or change the specificity of the protein with respect to this reaction, have a similar effect on its character as an anaphylactic antigen.

There is, again, a suggestive similarity between the limits of the specific discrimination shown by the two types of reaction. Both discriminate clearly between analogous substances, as for example the respective blood sera, from different species; but in neither case is the distinction absolute. In both cases there is a blurring of the distinction, an overlap of the specificity, when dealing with sera from related species; and the higher the degree of sensitiveness of the animal, or the more intense the precipitating quality of the immune serum, the greater the extent of the non-specific reaction. An animal which has received a previous injection of horse-serum acquires a high degree of sensitiveness to that serum, and usually shows no abnormal reaction to similar doses of ox or sheep serum; but when the sensitiveness to horse serum is very pronounced, the animal may react in a minor degree to large doses of serum from the ox or sheep.

Not only substances from different species, but the constituents of different organs, and even different individual proteins from the same organ, behave as separate antigens, distinguishable either by the anaphylactic or the precipitin reaction, though the discrimination is, again, not absolute in the case of either reaction. Wells was able to distinguish separate antigenic properties by the anaphylactic reaction in five different proteins from the hen's egg. Hartley and I worked with the three separate pure proteins from horse-serum, euglobulin, pseudoglobulin and albumin and found that they were similarly distinguished by the anaphylactic reaction in the guinea-pig, the distinction being very similar to that found by Andrew Hunter by means of the precipitin reaction. Still more suggestive of an identity of the anaphylactic antibody and the precipitin is the observation that serum from a rabbit, in which a strong precipitating reaction for a certain protein

has been produced, if injected into a normal guinea-pig, will render the latter anaphylactic to the same protein; and that the more powerful the precipitating quality of the rabbit's serum, the smaller the dose needed to produce a given degree of the specific sensitiveness in the guinea-pig. Strongly, however, as all such comparisons suggest an identity or close association between the anaphylactic antibody and the precipitin, it is not possible to regard anaphylaxis as due merely to the presence of precipitin in the blood. The serum from an anaphylactic guinea-pig forms no visible precipitate with the sensitizing antigen in any dilution. It is difficult, indeed, in the guinea-pig, so easily and regularly rendered anaphylactic, to obtain a precipitating serum; whereas the rabbit, which so readily yields a precipitating serum, is sensitized with relative difficulty and irregularity. By repeated injections, at intervals too short to allow the development of anaphylaxis, a precipitating quality may be induced in the guinea-pig's serum; but the animal is then not anaphylactic, but *immune*.

This, sketched with necessary brevity and in barest outline, omitting, perforce, details of the enormous mass of published experiments or reference to their authors, is the essence of the problem of the anaphylactic condition, as it presents itself to me. The two points which I ask you to bear in mind are (1) that anaphylaxis is a condition in which a normally innocuous, indeed, an inert substance has the effect of an acute poison of the type whose action we endeavored to analyze yesterday; (2) that the condition is apparently dependent on the formation or introduction of a specific antibody of the precipitin type; but that, when the abnormal sensitiveness is most clearly and characteristically developed, no precipitating quality is recognizable in the blood serum.

There are two lines along which these puzzling and seemingly contradictory indications can be explained. Both have been followed, by different writers and investigators. One of the earliest conceptions of the difference between anaphylaxis and immunity, put forward by Besredka and at one stage adopted by Friedberger, supposed that in the anaphylactic animal the antibody was fixed to the cells of the tissues, so that its interaction with the antigen occurred in the cells, whereas a sufficient excess of antibody in the circulating fluids fixed the antigen before it could reach the tissues, and thus produced immunity. Such a conception gives an intelligible explanation of the relation and difference between anaphylaxis and immunity. I still believe it to be fundamentally true, and propose presently to put before you evidence which seems to me to speak very strongly in its favor. It is incomplete, however, in that it does not immediately provide an explanation for the very remarkable resemblance between the anaphylactic shock and the action of naturally poisonous protein derivatives.

This resemblance formed the starting point for another type of theory. I believe Professor Vaughan was, at any rate, one of the earliest observers to put forward the idea that the anaphylactic condition depends on the production of a highly specific ferment, capable of hydrolysing the particular protein

to which the animal had been rendered sensitive, and no other. On this view, when the sensitizing protein is reinjected, the specific ferment immediately begins to split it, liberating toxic cleavage products, and so causing the shock. In this form the theory is not likely, I think, to win permanent acceptance. It shares with Abderhalden's conception of the "Abwehrfermente" the defect that it postulates the existence of ferments having a more specific relation to a protein substrate than any known ferment has been found to possess. A ferment which will hydrolyse horse protein, but not attack sheep protein is something quite different from ferments as we know them. Mere quantitative considerations also make it very difficult to accept the view that the anaphylactic shock is due to such fermentative cleavage of the antigen itself in the blood-stream. The dose of a pure protein, which suffices to kill a guinea-pig rendered anaphylactic to it, is much smaller than the fatal dose of the most powerful of the known poisonous protein derivatives producing this type of action. One twentieth of a milligram of pure egg albumen will kill a guinea-pig rendered sensitive to it; it requires about 10 times that dose of histamine, the most powerful of the known poisons of this class. Different attempts have been made to bring this theory of the fermentative production of a poison in the blood into harmony with the specificity of the anaphylactic reaction, and its apparent relation to the precipitin phenomenon. Friedberger supposed that the complex of antigen and antibody was formed in the blood, and there condensed upon itself a proteolytic ferment, somewhat gratuitously identified with the so-called "complement." He supposed that if the precipitating antibody were present in sufficient excess, hydrolysis took place so quickly as to overshoot the toxic stage, so that the animal was rendered immune.

Summarized thus baldly, but I think not unfairly, the theory seems somewhat fantastic, but it had a large influence on the course of the investigations devoted to this problem for several years. Its experimental basis was slight. Friedberger collected the specific precipitate, formed by the mixture of precipitating serum from a rabbit with its corresponding antigen, and digested this with fresh serum from normal guinea-pigs. The serum became toxic, and in some cases a dose of 4 or 5 c. c. of such treated serum caused death in guinea-pigs, with symptoms of the type supposed to be characteristic of the anaphylactic reaction. It was soon found, however, that "anaphylatoxin," as such toxic guinea-pig serum came to be called, could be prepared in many ways. If the serum was digested with suspensions of bacteria, or even with suspensions of kaolin or kieselguhr, it acquired a similar toxicity. Bordet found that digestion of guinea-pig serum with a small proportion of a sol of agar-agar would impart to it the characteristic toxicity, and Sachs and Nathan obtained similar effects by digesting it with starch or inulin. These phenomena of the so-called "anaphylatoxin formation" have attracted a very large share of the investigation devoted to anaphylaxis. Theories as to their meaning at the present time are of two chief kinds. In the first place Jobling and his co-workers, and also Bronfenbrenner, have published inter-

esting and highly suggestive series of studies on the relation between the natural trypsinic ferment, present in all serum, and the inhibitory factors, belonging to the so-called "anti-trypsin," which normally keep its activity in abeyance. They have described a number of physical or chemical agents which destroy or weaken this antitryptic power of normal serum, liberating the activity of its trypsinic ferment and initiating a self-digestion of the serum proteins. Such autodigestion renders the serum toxic, and it is supposed by this school of investigators that the formation of the complex of antigen and antibody, when the former is reinjected into an anaphylactic animal, has the function of removing antitrypsin from the sphere of action, thereby initiating autodigestion and the production of toxic cleavage products from the animal's own blood proteins. Such a conception successfully evades the quantitative and other difficulties attaching to the theory of a specific ferment digesting the antigen. It apparently fails, however, to account even for some of the most characteristic examples of anaphylatoxin formation *in vitro*. Incubation of serum with agar or starch does not bring about any perceptible hydrolytic cleavage of the proteins; but such serum, injected into a guinea-pig, reproduces the symptoms seen in the anaphylactic shock with far greater fidelity than serum in which recognizable autolysis has been induced by other forms of treatment. Another view has, therefore, gained adherents, which attributes the toxic action of serum treated with various colloids to some rather vaguely defined disturbance of the colloidal equilibrium of its proteins. Similarly the anaphylactic shock is attributed to a disturbance of the equilibrium of the colloids of the blood, brought about by the union in it of the antigen and antibody.

I make no pretence to do justice, in the limits at my disposal, to the mass of ingenious and careful experiments devoted to this phenomenon of anaphylatoxin formation. I attempt no judicial summary. I can only try to indicate to you the impression it makes on one who has devoted some thought and personal investigation to this problem of anaphylaxis. I believe that these observations on the production of toxic sera *in vitro* will in time find their place in the true conception of the anaphylactic reaction, but that their bearing on its meaning will not be of such a direct and obvious kind as has been widely assumed. I think an indication of the true position can be detected in the recent publications of Novy and de Kraif. It has long been known that blood, in clotting, acquires a toxic action of the general type to which I have so often alluded. In the serum, as it separates from the clot, this toxic action rapidly declines, but by no means wholly disappears. It can be revived and enhanced by various forms of treatment with absorbent suspensions or sols of colloidal substances. The weak point of the evidence, as a contribution to the theory of anaphylaxis, is the lack of clear connection between this artificial production of toxic serum and the anaphylactic reaction as seen in the living animal. If the production of "anaphylatoxin" *in vitro* really represented the process occurring in the circulation and causing the anaphylactic shock, the substances having this action *in vitro* should be even more effective when injected into the living circula-

tion; and, on the other hand, the most effective combination for producing anaphylatoxin outside the body should be that of serum from an anaphylactic animal with its corresponding antigen. In neither case, however, is this expectation fulfilled. Sols of agar and starch, which so readily and regularly make serum toxic, can usually be injected into the living blood-stream with impunity; and though Richet, Vaughan, Novy and some others have on occasion succeeded in producing a toxic mixture by incubating anaphylactic serum with antigen, such successes have been but rare exceptions among the predominant failures recorded by those who have tried this simple experiment. It can hardly be doubted that such an obvious and directly significant method of preparing "anaphylatoxin" would have been the usual one, if it gave any reasonable chance of success.

It seems to me, further, that the interest aroused by this work on the production of toxic sera has diverted attention from some of the essential features of the problem presented by anaphylaxis. Such experiments throw no real light on the difference between anaphylaxis and immunity; they do not touch on the characteristic and significant feature of passive anaphylaxis in the guinea-pig, namely, the fact that the introduction of the antibody into the circulation of a normal animal does not immediately render it sensitive to the corresponding antigen, but only after an interval of some hours. I know of no conception which throws any light on these essential features of the problem except that which relates the anaphylactic condition to a location of the antibody in the cells rather than in the blood-stream, and attributes immunity, on the other hand, to an excess of the antibody circulating in the blood. To the evidence in favor of this conception we may now return.

The evidence has been obtained along two lines. One was followed with great ingenuity and striking success by the late Richard Weil, by whose death during the war your country and this enquiry have lost an enthusiastic and brilliant investigator. Weil studied the phenomena of passive anaphylaxis, as produced in the guinea-pig by injecting a highly precipitating serum from a rabbit. He found, as others had done, that the sensitiveness did not appear immediately after the injection, even when this was given intravenously, but needed about 24 hours for its maximum development. By bleeding guinea-pigs at intervals after the injection, and injecting this blood into yet others, he was able to follow the fate of the antibody in the blood, and its relation to the development of sensitiveness. He found, in general terms, that sensitiveness only appeared as the antibody disappeared from the blood, and that only a small amount of antibody was left in circulation by the time the sensitiveness was fully developed. He found, further, that when the animal had thus become sensitive, a further injection of a large dose of the antibody had a protective action, rendering the animal temporarily immune. So far, then, the evidence obtained along these lines was completely in accord with the conception of anaphylaxis as due to predominant location of the antibody in the tissues, and of immunity as due to its presence in excess in the blood.

At about the same time this question of the location of the antibody was being attacked by an entirely different method. You will remember that in the guinea-pig the characteristic and dominating feature of the anaphylactic reaction is the contraction of the plain muscle of the bronchioles, causing an asphyxiating obstruction of the air-way. If this were caused by a reaction taking place in the muscle cells, without the intervention of the blood, the effect should be obtained with the plain muscle isolated from the body, and freed as far as possible from traces of blood. This was first attempted by Schultz, in Washington, who demonstrated the fundamental fact of the reaction of isolated intestinal plain muscle from

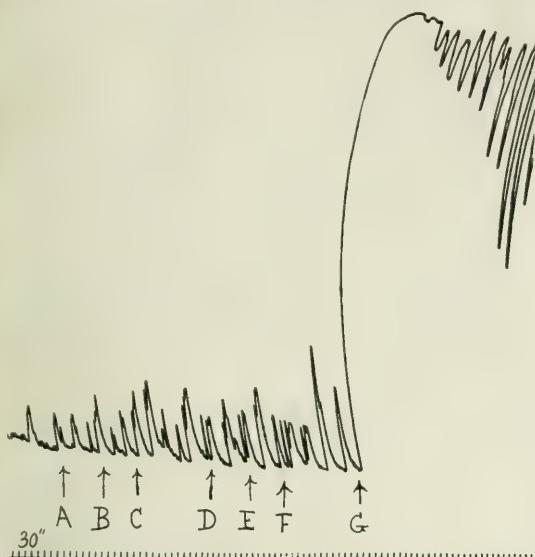


FIG. 1.—Sensitization: 1/400 c. c. antitoxin (horse)+1 test dose of toxin, 14 days. Doses in each case 0.1 c. c. A, sheep. B, cat. C, rabbit. D, dog. E, human serum. F, egg-white. G, horse serum. (Jour. of Pharm. and Exp. Therap., Vol. IV, p. 214, Fig. 26.)

the anaphylactic guinea-pig, when the specific antigen was added to the bath of Ringer's solution in which the muscle was suspended.

There were features of the method used by Schultz which made it somewhat difficult to disentangle the specific reaction to the antigen from the effects on normal isolated plain muscle of native sera, especially when fresh. My own attention had meanwhile been drawn accidentally to the same phenomenon. In connection with the work on histamine I was examining the action of a number of organ extracts and body fluids on the isolated uterine muscle of the guinea-pig. Certain preparations exhibited an astounding sensitiveness to horse serum, and enquiry elicited the fact that these were from guinea-pigs which had survived an antitoxin-standardization. As soon as I had the opportunity, I made a deliberate study of this phe-

nomenon, and found that it was possible to demonstrate all the characteristic phenomena of anaphylaxis on the isolated plain muscle *in vitro*. The sensitiveness exhibited was of great intensity, and highly specific; the reaction was obtained as well with highly purified proteins, devoid of action on the normal plain muscle, as with fresh sera; the plain muscle which had once been effectively stimulated by its specific antigen, had lost its natural sensitiveness, but could be resensitized *in vitro*. In fact, all the recognized phenomena of the anaphylactic condition could be demonstrated as easily on the isolated muscle, washed by prolonged perfusion from all removable traces of blood, as in the whole animal.



FIG. 2.—Sensitization: 1/540 diphtheria antitoxin (horse)+1 test dose of toxin, 14 days previously. Perfused. Bath volume 250 c. c. At A added 0.5 c. c. sheep serum. At B added 0.5 c. c. cat serum. At R (in this and all other figures) run off the fluid in the bath, wash out, and replace by clean Ringer's solution. At C added 0.1 c. c. horse serum. (Jour. of Pharm. and Exp. Therap., Vol. IV, p. 177, Fig. 1.)

The figures\* will indicate or recall the nature of the evidence obtained by this method.

Fig. 1 illustrates the close specificity of the reaction. A horn of the uterus from a guinea-pig which had received, fourteen days previously 0.0025 c. c. of horse serum was suspended in a bath containing 250 c. c. of Ringer's solution. At A, B, C, D, E and F were added doses of 0.1 c. c. of each of the following: sheep, cat, rabbit, dog and human serum, and egg-white. None produced any change in the low tonus and small natural rhythm exhibited by the muscle. At G 0.1 c. c. of horse serum was added, and the plain muscle promptly responded with maximal tonus.

Fig. 2 shows the reaction of plain muscle from a similarly sensitized guinea-pig. The uterus was, in this instance, perfused for an hour with warm Ringer's solution before removal from the body for experiment. It gives no response to 0.5 c. c. of sheep serum, added at A, or to 0.5 c. c. of cat serum at B,

\* Shown in the lecture as lantern slides.

but gives the characteristic maximal tonus in response to 0.1 c. c. of horse serum, added at *C*.

Fig. 3 shows a record on a faster moving surface; the response to the specific antigen, added at *A*, is seen to begin within 10 seconds—a latent period as brief as that observed with the action of many stimulant drugs on the normal plain muscle.

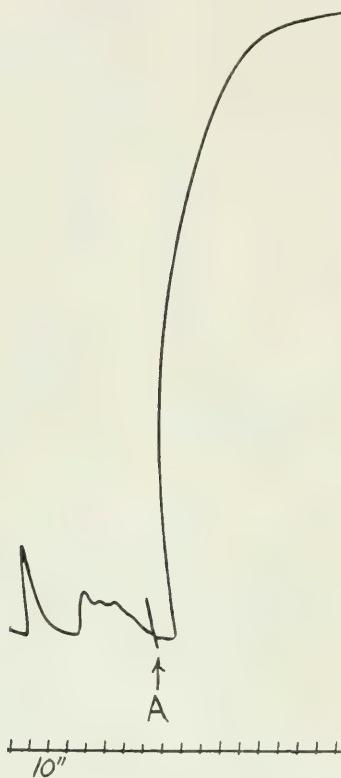


FIG. 3.—Sensitization: 1/480 diphtheria antitoxin + 1 test dose toxin, 14 days. Not perfused. Bath volume 250 c.c. Tracing taken with faster drum than that used in Fig. 2, to measure rapidity of onset of effect. *A*, 0.5 c.c. horse serum. (Journ. of Pharm. and Exp. Therap., Vol. IV, p. 178, Fig. 2.)

Figs. 4 and 5 illustrate several points. In the first place, the plain muscle is from a guinea-pig rendered *passively* anaphylactic to horse serum. The muscle has been thoroughly washed by perfusion, but still shows the characteristic response to 0.05 c. c. of horse serum, added at *A* to the 20 c. c. of Ringer's solution in which the muscle is suspended. After this effective stimulation, and a change to fresh Ringer's solution at *R*, the muscle is completely insensitive, responding as little as normal plain muscle to a second similar dose of horse serum added at *B*. After being washed again the muscle was soaked for 2½ hours in a 10 per cent dilution of serum

from guinea-pigs anaphylactic to horse serum, and then washed in numerous changes of clean Ringer's solution. The response to a further 0.05 c. c. of horse serum at Fig. 5, *E* shows that

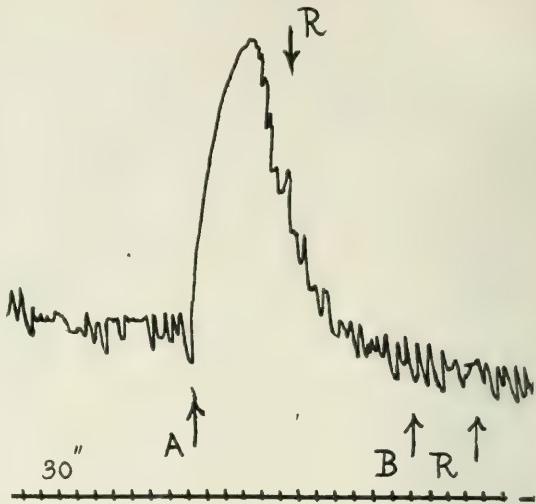


FIG. 4.—Passive sensitization with serum from guinea-pigs anaphylactic to horse serum (see test). Perfused. Bath volume 20 c.c. *A*, 0.05 c.c. horse serum. *B*, the same. (Journ. of Pharm. and Exp. Therap., Vol. IV, p. 198, Fig. 15.)

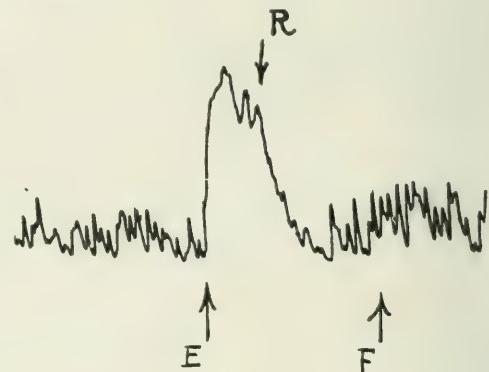


FIG. 5.—Same experiment as in Fig. 4. After resensitization *in vitro* by soaking for 2½ hours in 10 per cent serum from horse sensitive guinea-pigs. *E*, 0.05 c.c. horse serum. *F*, the same. (Journ. of Pharm. and Exp. Therap., Vol. IV, p. 199, Fig. 16.)

passive sensitiveness has been reconferring upon the muscle *in vitro*, and again removed by an effective dose of the antigen, since another dose of horse serum at *F* is without effect.

Other slides, not here reproduced, showed that the surviving plain muscle from a normal guinea-pig could be rendered

anaphylactic by prolonged perfusion with diluted serum from anaphylactic (or immunized) guinea-pigs. Such "passive sensitization *in vitro*" was hardly perceptible after one hour's perfusion, but was definitely in evidence after five hours' perfusion; a clear analogy to the first appearance of passive anaphylaxis *in vivo* four to six hours after intravenous injection of the anaphylactic or immune serum.

Fig. 6 illustrates the response of plain muscle from a guinea-pig rendered *immune* to horse serum by a series of suitably spaced injections of increasing size. Control guinea-pigs, treated in parallel with this one, received on the day of this experiment 5 c. c. of horse serum intraperitoneally, without showing symptoms of intoxication. It may safely be assumed, therefore, that the guinea-pig from which the uterus was taken

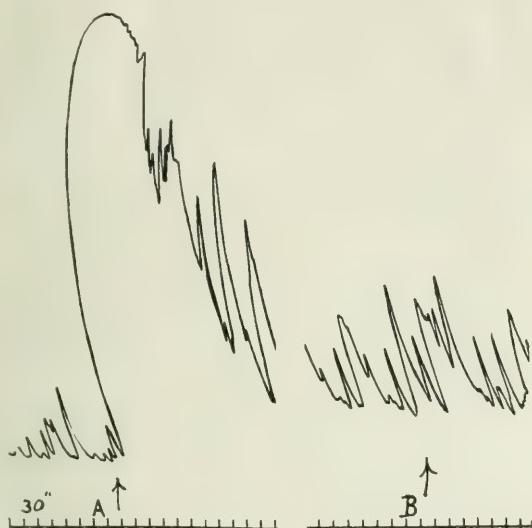


FIG. 6.—Guinea-pig immunized to horse serum. A, 0.5 c.c. horse serum. B (after change), 0.5 c.c. sheep serum. (Journ. of Pharm. and Exp. Therap., Vol. IV, p. 194, Fig. 13.)

was also immune. Nevertheless the plain muscle, washed carefully from blood by thorough perfusion, is found to be as highly sensitive to horse-serum, of which 0.5 c. c. was added at A, as that from many anaphylactic animals.

Since the serum from such immune guinea-pigs is much more effective in conferring passive anaphylaxis, on normal guinea-pigs, than a serum from those which are themselves actively anaphylactic, the conclusion seems to be inevitable that they owe their immunity to the presence in the blood of such an excess of antibody, that the antigen is fixed before it reaches the sensitive tissue cells. The sensitiveness of these can only be revealed, when they are washed clear from the protecting blood, as in this experiment, and brought into contact with the antigen *in vitro*.

The experiments make it clear that there are two ways in which the animal may lose a specific sensitiveness once

acquired. An effective, but not fatal, dose of the antigen will temporarily free the tissue cells from antibody, so that, until sensitiveness is reacquired, they have regained their normal indifference to the antigen; on the other hand, if injections be continued at suitable intervals, a condition is reached in which, though the tissues are sensitive, they are protected by excess of circulating antibody. These entirely different conditions, the temporary "desensitization" and the much more lasting true "immunity" have been widely confused in the literature by the application to both of the awkward and misleading term "antianaphylaxis."

These observations on isolated plain muscle, which have been abundantly confirmed by others, seem to leave no escape from the conclusion that the specific sensitization of the guinea-pig's tissue cells, by the presence in them of the antibody, is a reality, and that a true anaphylactic reaction is obtainable without the intervention of the blood at all. The same conclusion is indicated by the work of Coca, who showed that practically the whole blood of an anaphylactic guinea-pig could be replaced by blood from normal guinea-pigs without materially affecting the animal's reaction to the sensitizing antigen. Rumpf also, by an ingenious method of measuring the metabolic activity of the liver cells, showed that these cells in the anaphylactic guinea-pig were directly poisoned by the antigen, irrespective of the presence of its own blood.

I think it may be taken as almost generally accepted that anaphylaxis in the guinea-pig is largely the result of this location of the antibody in the tissue cells, though there is some evidence, provided, for instance, by recent experiments of Manwaring, for believing that the presence of the blood, containing some antibody, is a factor in the shock. Indeed, since there must be an equilibrium of distribution of antibody between the blood and the tissue cells, it is not reasonable to suppose that the latter will retain their full complement of antibody if the blood is washed away. In other species the position is less clear. Manwaring, and later Voegtlin and Bernheim showed that in the dog the characteristic shock does not appear when the liver is excluded from the circulation. It has usually been supposed that this indicates an elaboration of toxic substances in the liver as the cause of the shock, but Weil's experiments on the localized effect of antigen injected into the blood going only to one lobe of the liver, seems to indicate that here also we are dealing with a case of cellular sensitization.

In the rabbit, on the other hand, the evidence as yet available is predominantly in favor of the shock being due to an interaction of antigen and antibody in the blood. This animal, however, occupies in many respects an anomalous position. It is unique in the readiness with which the presence of precipitating antibody in its blood can be evoked; it is rendered sensitive with relative difficulty and uncertainty; it shows no clearly marked distinction between the conditions of anaphylaxis and immunity; it cannot be desensitized by a non-fatal reinjection, or rendered passively sensitive.

Let us confine our attention, for the moment at the least, to the phenomena in the guinea-pig, in which animal they

have been thoroughly studied, and in which their meaning is relatively clear. We have arrived at the conception of anaphylaxis in this species as due to the interaction of antigen and antibody occurring in the cells. We are still faced, however, by our initial problem. We have still to ask why the occurrence of this interaction in the cells should produce effects on plain muscle and capillary endothelium closely resembling those produced by a group of protein-derivatives, of which we took histamine as a type. The resemblance is too striking to be merely accidental; there must be some community of cause determining the community of result.

We are venturing now beyond the region of experimental observation into that of speculation, and there is abundant room for difference of opinion. It is largely a matter of balancing probabilities, or of choosing that conception which involves the smallest number of assumptions, or which is most fruitful of suggestion for further experiment. In endeavoring to find a common factor we may proceed in either direction; we may endeavor to interpret the anaphylactic reaction in terms of what we know of the action of poisonous protein derivatives, or we may endeavor to interpret the action of these normally poisonous substances in the light of what we know of the nature of the anaphylactic reaction. In a general way these alternatives correspond to the two types of theory I have already mentioned, which I may call the "proteolytic" and the "physical" theories of the anaphylactic shock. Let us consider the former, which attributes the resemblance between the anaphylactic shock and the effects of poisonous protein derivatives to an actual production of such derivatives in the anaphylactic reaction, the union of antigen and antibody being supposed in some way to determine the onset of a protein cleavage. In the light of the further evidence we have considered, this process must be transferred from the blood to the functionally vital cells, and this transfer makes the theory less difficult to accept. The supposition that the poison is produced in close contact with the reacting structures, largely if not wholly, removes, as Professor Abel has recently pointed out, the difficulty of harmonizing this theory of the fermentative production of a poison with the practically immediate onset of the symptoms, or of the response of the isolated tissue. I think, further, that there can be little doubt that the union of antibody and antigen is actually the prelude to a proteolysis. There is good evidence that the reinjection of a foreign protein, into an animal which has had previous injections of the same, is followed by an additional excretion of nitrogen in the urine, much in excess of that which could be derived from the antigen. On the other hand, the magnitude of this excess of nitrogenous output, representing excess of protein breakdown bears no kind of relation to the severity of the symptoms caused by the injection; it is greater in the immune animal, which shows no symptoms, than in the anaphylactic. I think, therefore, that the most that can be said for the proteolytic theory is that, if the injection of the antigen into the anaphylactic animal were to cause the liberation of protein cleavage products, or even of histamine, as Professor Abel seems to think not improbable, within the

active cells of the body, the result might well be such a reaction as we see in the anaphylactic shock.

The other, which I may call the physical hypothesis, starts from the fact that treatment of serum by brief incubation with various colloids imparts to it a toxicity of the type we are considering. The process is accompanied by no cleavage of proteins perceptible by chemical means. Bordet has supposed that some protective or inhibiting substance is removed, and a latent toxicity unmasked; others, in vaguer terms, that the equilibrium of the colloidal solution is upset. Whether this change in the state of aggregation of the blood colloids is to be pictured as transmitting itself to those of the cell plasma is not clear. In any case it is not unreasonable to suppose that a change of this kind, which can excite a reaction in cells even when it takes place in body fluids brought into contact with them, would be even more effective if it occurred in the cells themselves. Now it is just a change of this kind, a change in the state of aggregation of the colloids, which is the one event which we are entitled to assume, with some confidence, as occurring in the protoplasm of the anaphylactic cell when specifically precipitating antibody there meets the corresponding antigen. So far as we know anything about the nature of the action, it is this. Langley, following Ehrlich, has accustomed us to visualize the relation of an active chemical substance, or drug, to the cell whose activity it modifies, by speaking of a "receptive substance" in the cell, for which the drug has a specific affinity. In the case of the ordinary drug action the existence of the receptive substance is a convenient hypothesis, summarizing certain observed facts. The action of the antigenic protein on the cell rendered anaphylactic to it, however, provides the one instance of a receptive substance which can be identified in the precipitating antibody. We have seen how this can be attached to and detached from the cell. It can be obtained in solution apart from the cell, and its mode of interaction with the drug, in this instance the sensitizing antigen, can be studied in the test-tube. When this receptive substance, *i.e.*, the precipitin is mixed with a high dilution of the drug, *i.e.*, the antigenic protein, a change takes place; the colloidal complexes undergo a change in their state of dispersion, run together and ultimately form a flocculent precipitate. We must suppose that if the precipitin is in the protoplasm of a cell, and there meets the antigen to which it is specifically adjusted, a change in the state of dispersion of the protoplasmic colloids results. Now it is not impossible that such a change should initiate a fermentative change, leading to the formation of a substance having the histamine type of action or even of histamine itself. But we should still have to ask how histamine itself acts; why its production in the plain muscle cell, for example, should produce tonus. Of this, I venture to say, we know nothing. And in the existing state of our ignorance, it seems to me that the logical procedure is to interpret the unknown mode of action of these poisonous products from proteins in the light of what we do know concerning the mode of action of the specific antigen on the anaphylactic tissue; to suppose that histamine and the other substances having this

type of action also produce their action by initiating a change in the state of dispersion of the protoplasmic colloids; that it is a change of this kind, which, in terms of the different physiology of the different types of cell, causes contraction of the plain muscle, slackness and permeability of the capillary walls, and the whole group of phenomena which, with varying prominence in different species, constitute the complex which

we know as the anaphylactic shock, and which histamine and the poisonous protein derivatives so faithfully reproduce.

This is the conception of the nature of the anaphylactic shock, and of its relation to the action of a group of natural proteinogenous poisons, which seems to me at present to be at once the most economical of hypothesis, and the most fruitful of suggestion for further investigation.

## THE NATURAL HISTORY OF TYPHOID FEVER IN BALTIMORE, 1851-1919\*

By WILLIAM TRAVIS HOWARD, JR.

### THE WRITER'S STUDIES ON TYPHOID FEVER IN THE HEALTH DEPARTMENT

I entered the Health Department in the fall of 1915 and inherited the typhoid fever problem among others from Dr. Jones. The mortality rate per 100,000 for that year was 21.90. During 1916, I could not devote the necessary time to detailed study of histories of individual cases, but I was able to prepare the way for more complete histories than had before been obtainable and to take up more actively than had hitherto been practicable the study of the distribution of cases by five-day periods through a series of fifteen years, as well as to push the investigation of the relation of carriers to milk and to household and institutional epidemics. The latter work confirmed what was already known in the Health Department, that the bulk of the cases and deaths were reported in the summer and fall months, the peak coming usually late in August or in September, the fall in the autumn being gradual, and the rise and fall of the peak extending, as a rule, from July 15 to November 15. There was in the fifteen years rarely any evidence of a marked rise in spring, associated with freshets and so characteristic of the Great Lakes cities. With the greater facilities and leisure for this purpose than anyone had hitherto enjoyed, I set seriously to work in 1917 to determine, if possible, the most important sources of typhoid infection under the present conditions. The task was the easier because the number of reported cases to be investigated, as well as the number of deaths, had greatly diminished. The city officials, as well as the citizens, were greatly disappointed that typhoid fever had not almost completely disappeared after the new sewerage system and new water purification system were brought into use. It will be recalled that in the fall of 1915 the new water supply had become available and most of the connectible houses had been connected with the new sewerage system.

When my studies of typhoid fever in Baltimore began in 1916, it was estimated that about 60 per cent of the milk sold in Baltimore was pasteurized more or less efficiently. Some of these milk plants were well operated, both as to pasteurization of the milk and cleansing and sterilization of the milk utensils, including bottles and cans. In many of the pasteuri-

izing dairies, including some of the largest, there were glaring faults. Most of the plants used the *holding system*, and on the whole their results were better than in those depending upon the *flash system*. In some of these latter plants, notably in one in which the proprietor did the pasteurizing himself, the results were very good. Many of the plants were not only hopelessly dirty and unscreened, but were structurally unfit for their purpose. The supervisor of pasteurizing dairies and his assistant, who overlooked these plants for the Health Department, were not only well trained but diligent and tactful. Their supervision consisted of general inspection, the inspection of automatically registered temperature charts, the insistence on proper cooling of milk, and the cleanliness of plants and utensils. They submitted a large number of samples of raw and pasteurized milk to bacteriological examination and spent much time in instruction. They won the cooperation of many of the dairymen, and beyond question, they did much to lift milk pasteurization from a purely commercial basis to a method of disease prevention. A large part of both the pasteurized and raw milk sold was delivered in churns, from which the milk was dipped with hand dippers for domestic use. Much of the milk sold in small grocery and milk stores was similarly served to customers. The condition of the churns and of the refrigerators in many of these stores beggars description. The regulation of the Health Department forbidding milkmen from removing bottles from houses harboring cases of communicable diseases until the bottles have been disinfected by the Health Department was being obeyed. The inspection of milk on its arrival in town to guard against skimming and watering was fairly well covered, as had been the case since the procedure was instituted in 1894. The far reaching system of dairy farm inspection with its cooperative relation with the deputy state medical officers, inaugurated by Drs. Jones and Blanck, was being carried out as well as could be expected.

The anti-typhoid work of the Health Department was extended in 1916 by a search for carriers in households, in restaurants and oyster-shucking establishments, and in connection with dairies and dairy farms. A canvas was made of restaurants, dairies, and dairy farms for workers who had typhoid fever. From the large number of such persons thus apprehended, routine cultures of the bowel and bladder dis-

\* Continued from the August number of the Bulletin.

charges were made. Two carriers were found among dairy employees within the City. To one of them 10 cases of typhoid fever were traced. The other was a driver in a milk wagon who only handled the milk after it was bottled and to whom no cases of typhoid fever had been traced. Both were withdrawn from milk work. Workers on dairy farms suspected of being carriers, either came to the laboratory to furnish the desired specimens for culture, or the specimens were collected by the deputy state health officers. Two suspected carriers who had had typhoid the year before refused to be cultured. An epidemic of 24 cases of typhoid fever among the users of the milk from the dairy farm on which they lived subsided at once after the milk from this farm was excluded from the City. A total of 34 cases of typhoid fever was traced to milk during 1916. Four cases in one household and 1 case in another were traced to one carrier, a butler who had had typhoid fever fifteen years before. Nine cases in a college were traced to a female cook in a restaurant who proved to be a carrier. Another carrier, a cook in a private family, was apprehended. To her were attributed 2 cases of the disease, one occurring in 1914 and the other in 1915. In all, eight carriers were apprehended in 1916. Including the milk epidemic presumably due to one or two carriers on a dairy farm, nearly 30 cases of typhoid were traced to carriers this year.

All the remaining wells within the City were investigated by chemical and bacteriological methods, and quite a number showed evidences of pollution and were closed. Dr. Stokes isolated *B. typhosus* from the water of one such well that had been suspected as the source of infection of 4 cases of typhoid fever. A number of wells at roadside and fishing resorts near the City, frequented by Baltimoreans, were found to be polluted and reported to the State Board of Health.

One hundred and twenty-five cases of typhoid fever were classified as "infected out of town." Some of these were residents of the City who had contracted the disease while away for work or pleasure—many of them at summer resorts. Nine out of fifteen members of a baseball team developed typhoid fever after drinking water from a known polluted source at Grafton, West Virginia. Of the 110 Baltimoreans infected outside the City, 101 were infected in rural Maryland, and of the whole number of such outside infections, 106 occurred in the period of greatest incidence of the disease, as follows: July, 19, August, 23, September, 16, and October, 18.

Of the 776 reported cases, a satisfactory explanation of the source of infection was traced in 178, or nearly 22 per cent.

In addition to a search for carriers, attempts were made for better control of the milk supply, the elimination of polluted wells, and the prosecution of the fly nuisance through the newspapers, various civic bodies, certain insurance companies, the Street Cleaning Department, the health wardens, the nurses, and the Police Department. Instructions as to how to avoid typhoid fever, both at home and abroad, and urging anti-typhoid inoculations were not only distributed in the homes of cases of the disease, but through the medium of the newspapers, and circulars left in the houses. The

latter was accomplished very largely through the collecting agents of industrial insurance companies. Physicians were requested to urge the general use of anti-typhoid vaccine, especially in households with recent cases of disease. The time was ripe this year, too, to prosecute the grading and smooth paving of the private alleys of the City, so long a nuisance in promoting the breeding and feeding of flies. This work, begun in 1916, was more than half completed with the paving of about one half of the 3000 such alleys, when the work was temporarily abandoned on account of the war.

In 1917, the mode of infection was more or less convincingly traced in 225, or 41.17 per cent of the total number of 544 reported cases. The seasonal distribution of both cases and deaths remained relatively the same as in previous years. One hundred and forty-two, or 26.10 per cent of the reported cases, were classified as infected outside of the City (14 of these came from ships); 75, or 13.78 per cent of the total number of cases, were infected in rural Maryland; and 53, or 9.74 per cent, contracted the disease in other states. Table 4

TABLE 4  
IMPORTED CASES AND OUT-OF-TOWN INFECTIONS, 1917

Maryland counties	Other states
Baltimore .....	29
Anne Arundel .....	15
Kent .....	9
Harford .....	4
Worcester (Ocean City) .....	4
Caroline .....	3
Frederick .....	3
Dorchester .....	2
Carroll .....	2
Charles .....	1
Prince George's .....	1
Wicomico .....	1
Allegany (Cumberland) .....	1
	Massachusetts .....
	Maine .....
	West Virginia .....
	Delaware .....
	North Carolina .....
	New York .....
	New Jersey .....
	Pennsylvania .....
	Virginia .....
	Ships .....
75	1
	2
	3
	3
	7
	9
	13
	13
	53
	14
	67
	75
	142

gives the distribution of these cases according to counties and according to other states. A considerable number of the 13 cases attributed to Pennsylvania occurred in non-residents of Baltimore, who came here for medical treatment or for work and who were either sick at the time of their arrival or became so within a day or two thereafter. Of the 13 cases attributed to Virginia, 4 were among Baltimoreans who became sick at Virginia Beach, and several other patients came to Baltimore from Norfolk or Portsmouth to hospitals for medical treatment. Of the 75 cases attributed to rural Maryland, a very large proportion (44) contracted the disease while sojourning in Baltimore and Anne Arundel Counties for work or on vacation. Nearly all of these cases occurred in the warm weather, when typhoid fever is most prevalent in the country districts. Of the total number of cases, 43, or 7.9 per cent, were traced to milk, there being three clear cut milk epidemics during the summer, all of which were traced to infection of the milk in dairies within the City. In 15 cases, a history of contact with recent cases within the household was obtained,

and in 6 further cases the infection was traced to hospitals in Baltimore, making a total of 21, or 3.85 per cent of cases traced to contact with clinical cases of typhoid fever. Fifteen cases occurred in families in which one or more members, occasionally unrelated inmates, had had typhoid fever one or more years before—the interval ranging from thirty years to one year. These previous cases of typhoid fever occurred in mothers, five times; grandmothers, twice; sisters, twice; brothers, four times; and fathers and wives, once each. In several of these families, there had been repeated cases. In two of the fifteen families, carriers were demonstrated by culture methods. One of these families is of particular interest, there having been, during a period of seventeen years, four outbreaks of typhoid fever in three generations with a total of 8 cases. The grandmother had contracted the disease seventeen years before; the next year, her two sons, her son-in-law and daughter and an unmarried daughter, all living in the same house with her, developed typhoid fever. In June, 1916, this woman's grandchild, aged 7 years, who lived in her house, developed the disease. On January 2, 1917, a second grandchild, a sister of the first, was reported as a case of typhoid fever. The whole family was cultured on January 8, 1917, and the grandmother, the unmarried aunt, and the child who had had typhoid fever in June of the previous year, were all three found to be carriers. Another carrier was found in the person of the mother of a boy who had had typhoid fever the previous year. In this year, eleven additional proven carriers were added to the Health Department's list, making a total of nineteen carriers under observation. In connection with contact infection, 4 cases gave a history of having had typhoid fever before, and it is suggested that these were examples of self-infection. One of these cases occurred within eight months, and a second within twelve months of the primary attack. One of the cases was treated in both attacks at the Johns Hopkins Hospital, the first attack occurring in August, 1908, and the second in January, 1917. In the fourth case, the attacks were six years apart.

In 1917, the morbidity rate per 100,000 was 83.79. Notwithstanding the fact that 24 deaths, or 26 per cent of the total of 92 deaths, occurred among typhoid fever patients brought to Baltimore hospitals for treatment from rural Maryland, the mortality rate fell to 14.17 per 100,000. There were 152 cases officially recorded by the State Board of Health against the counties from which they came, among whom the cases fatality rate was 15.85 per cent. The annual case fatality rate, excluding the above, but including cases and deaths of persons from other states than Maryland, was 11.75 per cent.

In 1918, there were 302 cases and 73 deaths from typhoid fever, a decrease of 45 per cent in the cases and 28.7 per cent in the deaths as compared with 1917. The distribution of cases and deaths by months followed the same course as in previous years, with the exception that during October, the period of the influenza epidemic, the number of deaths from typhoid fever was disproportionately high, there being a total of 17 deaths for this month against 11 in September and 1

each in November and December. The number of out of town infections of Baltimore residents on trips, and of imported cases, was 53, or 17.55 per cent of the whole. In 39 cases, or 12.58 per cent, infection was attributed to contact with recent cases in the households. Five cases in one family were traced to a carrier and there was one case of laboratory infection. In addition to these, 16 cases were probably infected outside the City, and in 20 cases this mode of infection was a possibility. Twenty-two cases, or 7.9 per cent of the total number, resided in the same house with persons who had had typhoid fever previously, at times varying from thirty years to one year. Of the 24 possible infectors for this group of cases, there were 16 females and 8 males, but 2 of the possible male infectors were associated with possible female infectors in the same house; that is, in two of the households, the father and sister of the patients had had the fever. The 16 possible female infectors showed the following relationships to the patients: mother in 9 cases, sister in 3, wife in 1, unrelated female in 3 cases. The relation of the male infectors to the patients was: father alone, twice; father with sister, twice; brother, twice; husband, once; unrelated male, once. One father, upon whom the carrier state was proven by culture, was probably responsible for 5 cases among his children. In the latter part of July and the early part of August, the five children of a police officer came down in rapid succession with typhoid fever. The father, who had had typhoid fever fifteen years before, proved on culture to be a fecal carrier. No other source of infection for these children was ascertainable. A large proportion of these probable carriers were cultured, but only the one above mentioned was proven to be a carrier. Two additional carriers, to whom no cases were attributed, were apprehended. This year again, 4 cases presented a previous history of having had typhoid fever. The case of laboratory infection occurred in a medical student who swallowed typhoid bacilli sucked up through a pipette from a bouillon culture while working in a bacteriological laboratory.

The morbidity rate fell to 45.82 and the mortality rate to 11.08 per 100,000. Fourteen, or 19.18 per cent, of the 73 deaths from typhoid fever registered against Baltimore occurred among patients from rural Maryland sent to the Baltimore hospitals for treatment. There were 94 such cases against the 152 in the previous year. The case fatality rate among these cases was 14.9 per cent. During 1918, there were 59 deaths from typhoid fever properly chargeable to Baltimore, giving a case fatality rate of 17.2 per cent. As previously pointed out, the case fatality rate was influenced in great degree by the influenza epidemic in October, when there were 17 deaths among typhoid fever patients.

In 1919, there was a large annexation of territory, in part closely built up, with a population for which no accurate figures are as yet obtainable. On the basis of the police census taken in the spring of 1919, it was estimated at 73,000, the proportion of negroes being much smaller than in the old City. The Bureau of the Census authorized the Health Department, for statistical purposes, to add about 60,000 for the annexed territory to the estimated population of the old

City. As the inclusion of this territory and its unknown population in the last year of the series would make accurate comparison of the course of the disease in former years impossible, for the purposes of the present study, the figures for the old City (old twenty-four wards) and for the Annex (new four wards) have been kept separate. The figures used in the graph are those derived from the old twenty-four wards. The problems of typhoid fever in the annexed territory will, therefore, be considered separately.

In the old twenty-four wards, the distribution of cases and deaths by months did not vary materially from the usual. Of the 293 reported cases, the modes of infection were traced as follows: 50, or 17.06 per cent, including definite imported cases in non-residents of Baltimore, and Maryland outside of Baltimore, were infected outside of the City; 36, or 12.78 per cent, occurred as secondary infections from recent previous cases in households and hospitals; 12, or 4.09 per cent, were infected by polluted wells and streams (2 cases were traced to wells at Curtis Bay and 10 to drinking the water of Gwynn's Falls); and 2 cases, or 0.67 per cent, were traced to laboratory infection. A total of 100 cases, or 34.05 per cent of the whole, were explained with reasonable certainty. A probable explanation was obtained for 52, or 17.73 per cent of the cases: 23, or 7.84 per cent, due to infection from remote cases in households; 5, or 1.70 per cent, due to neighborhood infection (from recent cases, probably through the medium of flies); and 23, or 8.19 per cent, due to infection outside the City. In addition, there were 14 cases, or 4.74 per cent, that were possibly infected outside the City. Altogether, an explanation, more or less satisfactory, of the mode or source of infection was obtained in 166 cases, or 56.52 per cent.

The cases attributed to infection from Gwynn's Falls occurred in ten children, members of a Sunday School in Southwest Baltimore (twenty-fourth ward) who took part in a picnic at Gwynn's Falls Park. Some twenty of the children went wading in Gwynn's Falls and, the day being very warm, drank the water of this stream. The cases of typhoid fever were restricted to those who so used the stream, and careful inquiry revealed no other source of infection. Half of those exposed to this source developed the disease. The stream at this point receives a considerable body of household sewerage, and there had been cases of typhoid fever in this area during the summer. The stream is also open to serious pollution above this point. It is of interest, that, as in 1918, no cases of typhoid were traced to milk. Two carriers were apprehended, making a total of twenty-four under restriction by the Health Department.

The morbidity rate was 43.79 per 100,000. There were 49 typhoid deaths in the old city, including 8 non-residents infected outside the City of whom 5 were from rural Maryland. The mortality rate was, therefore, 7.21 per 100,000. The mortality rate, less the 5 deaths among the 34 cases brought from rural Maryland to Baltimore hospitals for treatment, but including 3 other deaths of non-residents (a seaman, a person from Delaware, and another from West

Virginia), was 6.58. The mortality rate among Baltimoreans alone was 6.28. The case fatality rate, based upon the 49 deaths occurring in the old twenty-four wards, and especially chargeable against Baltimore, was 16.72 per cent. The case fatality rate among the 34 cases from rural Maryland brought to Baltimore for medical treatment was 14.80 per cent. The case fatality rate for Baltimore minus these 5 deaths was 15.01 per cent. A more accurate picture of the case fatality rate, however, is obtained by dividing the whole number of cases reported in Baltimore in 1919 into the total number of deaths occurring among these cases not within the calendar months, but within a reasonable time afterwards. Of the 293 cases reported 41 died within the year 1919 and 3 between January 1 and May 1, 1920—a total of 44—giving a case fatality rate of 15.01 which happens to be exactly the same as that obtained when the deaths of patients from rural Maryland were left out of consideration. Approximately the same case fatality rate (14.80 per cent) is obtained by dividing the total deaths, including those of all non-residents dying in Baltimore, by the total number of cases reported in Baltimore, plus the cases brought into the City from rural Maryland for treatment ( $293+34=327$ ). It would appear that a case fatality rate of about 15 per cent is correct for Baltimore (old twenty-four wards) in 1919.

Just as in the annexation of 1888, so in that of 1919 the City annexed a territory, much of which was characterized by insanitary conditions and with a high typhoid rate. In certain parts of this area, as in Roland Park, sanitary conditions were better than in the City itself. According to data kindly furnished me by Dr. C. Hampson Jones, when Chief of the Bureau of Communicable Diseases of the State Department of Health, there were 128 reported cases of typhoid fever in 1918 in the area annexed in 1919. A large proportion of these cases, 48, were in Highlandtown; 31 were in Brooklyn; and 22 in Curtis Bay. There were 10 cases in Arlington, 6 at Mt. Winans, and 5 at Hullsville. The water supply of Highlandtown is derived from the grossly polluted Herring Run, but is treated with chlorine. Upon examinations made in the laboratories of the Baltimore Health Department during 1919, this water supply showed evidence of marked pollution. In at least one milk epidemic in Baltimore in 1917, studied by me, cases of typhoid fever occurred in Highlandtown among customers of the infected dairy in the old City. There is every reason to suppose that milk has in the past played at least as important a part in spreading typhoid fever in Highlandtown as in the old City. The sewerage system is as crude as it formerly was in Baltimore. Much of Brooklyn and Curtis Bay proper have pure water supplies, filtered water from the Patapsco in the former and artesian well water in the latter. Both are, however, in large part without sanitary sewerage disposal; privies and cesspools being still largely in use. Overflowing privies and cesspools are common. In the summer of 1918, there was an extensive milk outbreak of typhoid fever in Brooklyn and Curtis Bay, traced to a single dairy. Mt. Winans and Hullsville are comparatively small places, in which the water is derived

from ordinary wells, and the common privy is still in use. Many of the smaller villages and settlements in the north-western portion of the annex have pure water, supplied either from artesian wells or from the Avalona supply of the Baltimore County Water Company. Good water is served to Mt. Washington, Roland Park, a part of Arlington and Govans, and to a part of the developments on the Harford Road. In much of Arlington, Govans, and the settlements along the Harford Road, there are no proper sewers, and cesspools and privies are situated so as to pollute the wells from which drinking water is obtained. So, in much of the newly annexed territory, the City is confronted with insanitary conditions fraught with danger.

With the annexation, the City's laws and regulations in regard to milk became immediately applicable to the new wards, and fortunately in 1919 there were no milk epidemics. There was a total of 65 cases of typhoid fever reported in the four new wards in 1919, in comparison with 128 the previous year. Of the 65 cases in the Annex, 8, or 12.31 per cent were classified as infected outside of the City; 6, or 9.23 per cent, were attributed to contact with recent cases in households; the same number, to contact with remote cases; 12, or 18.46 per cent, to infection from wells or springs; and 2, or 3.07 per cent, to neighborhood infection, probably by flies. No cases were traced to milk. It will be noted that in the Annex a somewhat larger proportion of the cases were explained than in the old twenty-four wards.

On an estimated population of 65,000, there was a morbidity rate of 100 per 100,000. There were 9 deaths. The mortality rate was 13.84 per 100,000, and the case fatality rate was 13.84 per cent. The mortality rate of the new four wards was nearly twice that of the old twenty-four wards.

#### SUMMARY OF INFORMATION IN REGARD TO SOURCES OF INFECTION OF TYPHOID FEVER, 1916-1919

*Sources of Infection in Reported Cases.*—In Table 5, the results of the investigations of 1916 to 1919, inclusive, on the sources of infection of reported cases are set forth. It will be noted that the proportion of cases for which no explanation of the mode of infection is determined falls steadily from 1916 to 1919. This is to some degree due to the fact that in the first two years the data in regard to probable and possible outside infections, having been destroyed by fire, are lacking in the table.

Attention is directed to the very large proportion of cases certainly infected outside the City, varying from 16 to 26 per cent in the four years. These include the imported cases occurring among non-residents from other states or from foreign countries. The great bulk of them, however, are represented by residents of Baltimore who contracted the disease outside of the City while away for work or vacation. It will be seen that the percentage of cases infected outside of the City is fairly constant for this period. In addition to this group, there are two other comparatively large groups in 1918 and 1919, one in which infection outside of the City was probable but not certain, and a second in which it was

possible, due to the fact that the individuals had been out of town for one or two days only within three weeks or a month before the beginning of the illness.

The very much larger percentage of cases traced to contact with recent cases in households and hospitals in 1918 and 1919 over that of 1917 is undoubtedly to some extent due to more adequate histories obtained in the last two years. Cases were placed in this group only after the most critical consideration; no cases were so assigned unless there was a definite interval of a month or more between the beginning of the illness of the first and succeeding cases, or cases, and only when any other mode of infection could be excluded with reasonable certainty. A surprisingly large percentage of these

TABLE 5  
THE SOURCES OF INFECTION OF TYPHOID FEVER FOR 1916 TO 1919,  
INCLUSIVE

Sources of infection	1916			1917			1918			1919		
	Cases	Percentage of cases	Cases	Percentage of cases	Cases	Percentage of cases	24 wards cases	Percentage of cases	Annex cases	Percentage of cases		
Infected out of city, including imported cases.	125	16.14	142	26.10	53	17.55	50	17.06	8	12.31		
Contact with recent cases in households and hospitals.	...	...	21	3.86	39	12.58	36	12.28	6	9.23		
Contact with remote cases in households.	...	...	15	2.75	22	7.90	23	7.84	6	9.23		
Neighborhood infection.	...	...	-	...	-	...	5	1.70	2	3.07		
Springs, wells, and streams.	4	0.51	...	...	...	...	12	4.09	12	18.46		
Carriers.	14	1.50	...	...	5	1.65	...	...	...	...		
Milk.	34	4.52	43	7.90	...	...	...	...	...	...		
Laboratory.	...	...	...	...	1	0.33	2	0.67	..	...		
Self-infection.	...	...	4	0.73	4	1.32	...	...	...	...		
Probable outside.	...	...	...	...	16	5.22	24	8.19	8	12.31		
Possible outside.	...	...	...	...	20	6.26	14	4.74	1	1.53		
Unexplained.	507	77.13	319	58.83	142	47.02	127	43.34	22	33.84		
Total cases.	774	100.00	544	100.00	302	100.00	293	100.00	65	100.00		

cases occurred among individuals admitted to the general wards, or semi-private wards, of hospitals to be treated for other affections and who developed the disease three weeks or more after admission. In nearly all of these cases, definite, associative contact with typhoid fever cases in the wards could be traced, and in every instance there were cases of typhoid fever in these hospitals at the time of the patient's stay. These cases occurred in four large hospitals.

It will be noted that infection from springs and wells played an unimportant part, there being 4 cases traced to one polluted spring in 1916 and 2 such cases in 1919. In the latter year, there was an epidemic of 10 cases among children who drank the polluted water of Gwynn's Falls.

It is significant that in 1916 and 1917 a large number of cases in definite epidemics were readily traceable to infec-

tion through milk, whereas in the last two years, after the new milk ordinance was put into force, no cases were traced to milk.

The 3 cases traced to infection in bacteriological laboratories in 1918 and 1919 were, of course, fortuitous and have no important bearing upon the question under discussion.

Under self-infection are included the 8 cases noted in the four years, in which the individuals gave a history of having had typhoid fever before and which are included in the table as possibly explained cases. Concerning the possible importance of this source of infection, much can, of course, be said for and against.

There are included in the group under carriers, all cases in which infection through means other than milk is attributed to proven carriers. As will be seen later, although diligent search was made, comparatively few cases in households were traced to proven carriers during the last three years. Allusion has been made to the extensive investigation conducted since 1916 for the apprehension of possible carriers among food handlers. Including these and possible carriers in households, in the four years, 426 individuals were submitted to the test made by culture of both feces and urine. The methods in use for this purpose are those of the U. S. Army Manual; *i. e.*, cultures from fluid stools or from urine on Endo's medium. The work was done by Dr. Stokes or by Dr. Hatchel, or under their immediate supervision. Twenty-four, or 5.26 per cent of these individuals, were thus proven to be carriers. There are now, therefore, twenty-four carriers under control of the Health Department.

Attention was drawn to the importance of infection from remote cases in households when searching for carriers in households, in which, according to the histories of reported cases, a member of the household, almost invariably a relative, was said to have had typhoid fever at some remote date. While from time to time the carrier state was established in many of these suspects by culture, more often even repeated cultures from both bowel and bladder discharges were negative. As my experience with proven carriers, especially bowel carriers, grew, I was struck with the fact that, as tested by cultures made in the ordinary way, there was great intermittency of the carrier state. In the case of a urinary carrier, a butler, there was very considerable intermittence of the emission of the typhoid bacilli. This man served in one family for eight years before any of them developed clinical typhoid fever. Suddenly four were attacked in short order, and his own grandson, who had been living with him for some years, developed the disease at the same time. Further accumulated evidence showed that in a very large proportion of the cases occurring in individuals living in households with proven carriers this association had been going on for years. It seemed to me likely that the infection, or non-infection, of the exposed must be determined by something more than chance contamination of food or drink, under conditions favorable for the multiplication of the typhoid bacilli in such articles to a degree necessary to make an infective dose for the victim, even if it be assumed that the susceptibility of the

latter remained constant. Experience with typhoid carriers shows that in many instances at least a very favorable combination of circumstances, ruled to a very considerable degree by chance, must occur in order that they may successfully inoculate others with the typhoid fever disease. From my experience, it would appear that one of the factors involved in this combination is the intermittence of emission of the infective agent by the carrier. Another forcible factor must be the opportunity offered for infection by the character of the associative contact between carrier and victim. It is well known that carriers who handle food for others have better opportunities than have non-food handlers for transmitting typhoid organisms, at least in numbers adequate for producing clinical typhoid fever. Therefore, suspected carriers, the possible infectors of individuals living in households with them, should be shown to be peculiarly favorably situated in the character of their associative contact to transmit the infective agent, before any definite importance can be attached to them as the sources of infection. Unless this is done, and other possible sources of infection can be excluded with a reasonable degree of certainty, the association between cause and effect is based upon little more than suspicion. If it be shown that the emission of typhoid bacilli (as proved by the culture test) is intermittent among chronic typhoid carriers, and that the suspected carriers, supposed to be responsible for infecting household associates, occupy a relation in the household that favors transmission of the infective agent by food and drink and are in any large proportion of cases food handlers, the character of the evidence is raised to a much higher level.

Analysis of the observed cases during the three years, 1917 to 1919, inclusive, shows that of 68 such cases, including carriers and suspected carriers in households, 66.17 per cent were females, and the percentage of females to males was approximately the same in each year. (See Table 6.)

TABLE 6  
SEX DISTRIBUTION OF PROVEN AND SUSPECTED TYPHOID CARRIERS  
IN HOUSEHOLDS

Year	Number of persons	Females	Males	Percentage of females
1917.....	15	10	5	66.66
1918.....	26	18	8	69.23
1919.....	27	17	10	62.96
	68	45	23	66.17

The forty-five female carriers or suspected carriers bore the following relationships to the typhoid fever patients: Mothers, 24; sisters, 12; wives, 3; grandmothers, 2; aunts, 1; domestic servants, 3. The twenty-three males in question held relationship to the patients as follows: Fathers, 9; brothers, 9; husbands, 3; uncle, 1; unrelated male, 1.

Of the whole number in this group of sixty-eight suspected carriers, in only six cases was the carrier state established by culture.

The argument that these suspected carriers were, at the time of the infection of the individuals associated with them in their households, true carriers and responsible for spreading the disease is supported mainly by the facts; first, that in none of the cases of typhoid fever was any other source of infection traceable; second, that as determined by ordinary culture methods, known typhoid carriers often show marked intermittence of emission of typhoid bacilli in their discharges; and third, that there was a great preponderance among the suspected carriers of mothers and sisters and other females most likely to be food handlers.

If the inference that typhoid bacilli carriers, both fecal and urinary, are often intermittent in the discharge of typhoid

TABLE 7  
SOURCES OF INFECTION OF TYPHOID CASES FOR 1919

	Old 24 wards		Annex		City as a whole	
	No. of cases	Per-cent of cases	No. of cases	Per-cent of cases	No. of cases	Per-cent of cases
<i>Certainly explained</i>						
Imported .....	14	4.74	...	....	14	3.91
Outside certain .....	36	12.28	8	12.31	44	12.29
Recent contact, homes and hospitals .....	36	12.28	6	9.22	42	11.73
Laboratory .....	2	0.67	...	....	2	0.53
Gwynns Falls .....	10	3.41	...	....	10	2.79
Springs and wells .....	2	0.67	12	18.46	14	3.91
Total .....	100	31.06	26	39.90	126	35.16
<i>Probably explained</i>						
Remote cases .....	23	7.84	6	9.23	29	8.10
Neighborhood infection .....	5	1.70	2	3.07	7	1.95
Outside probable .....	24	8.19	8	12.31	32	8.93
Total .....	52	17.73	16	24.61	68	18.98
<i>Possibly explained</i>						
Outside possible .....	14	4.74	1	1.53	15	4.18
Total .....	14	4.74	1	1.53	15	4.18
Total explained .....	166	56.52	43	66.13	200	58.32
Total unexplained .....	127	43.34	22	33.84	149	41.62
Final total .....	293	100.00	65	100.00	349	100.00

bacilli be correct, it naturally follows that it is erroneous and dangerous in public health administration to conclude, on the basis of a single or even several negative cultures, that an individual who has had typhoid fever is not a carrier. It would rather seem that, in order that a typhoid carrier may infect others, among the other various elements of chance that must fall favorably is the one that the carrier be in a period of emission of the infecting agent. It is now well established that, in a typhoid bacillus carrier, cultures may show this organism in large numbers in material removed by a duodenal tube and yet none appear in fecal cultures taken at the same time. If this be the case with fecal carriers, even much more weight is to be placed upon the evidence at hand in support of the theory of intermittency of the discharge of typhoid bacilli in the case of urinary carriers, for it is a comparatively

simple matter to cultivate the typhoid bacillus, when present, from urine collected in a sterile container, for the chances of overgrowth of the typhoid bacillus by other organisms is slight, probably much less than is the case with material collected from the duodenum in bile-system carriers.

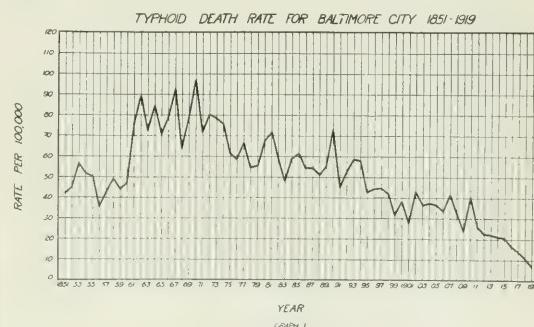
In Table 7, the results of the study of the sources of infection of the cases of typhoid fever, reported from the old twenty-four wards and the Annex during 1919, are set forth in greater detail.

#### STATISTICAL ANALYSIS

In this analysis, it is for the most part necessary to proceed under the assumption that the official figures of the Health Department for cases and deaths of typhoid fever are correct. It is realized that this assumption includes many sources of error. Unfortunately, the available data do not afford material upon which even approximate corrections may be based. The chief sources of error affect the period previous to 1890.

#### I. MORTALITY RATES

*Total Population.*—In Graph 1 are represented the annual mortality rates per 100,000 living population in Baltimore



from 1851 to 1919, inclusive. For the sake of more accurate comparison, the rate for 1919 has been calculated for the old twenty-four wards of the City. It will be noted in the graph that for the first ten years the mortality rate averaged about 45 per annum. In 1861, there was a decided increase in the rate which continued at about 80 until 1871, since which time there has been an irregular but decided fall.

These rates have been calculated from the reported deaths from typhoid fever alone, with the exception of the years from 1879 to 1898, inclusive, in which the deaths ascribed to "typhomalaria" have been included. If the rates calculated from the deaths from gastric fever be added to the rates given for typhoid fever on the graph, from 1851 to 1875 inclusive, (the years of our period during which gastric fever, which was very likely typhoid fever, played a prominent part as a cause of death), the course of the curve for typhoid fever could not be materially changed; it would simply mean adding rather uniformly from 5 to 10 to the mortality rate from 1851 to 1875. Any important influence of typhus fever on the curve

for typhoid fever is rather remote for two reasons: In the first place, though typhus fever occurred endemically in Baltimore until 1857, its course was marked by distinct epidemic waves, and the wave which began in the early 40's subsided in the early 50's. In the second place, the fact that typhoid fever was first recognized by the Health Department in 1851 suggests very strongly that by this time the diagnosis between this disease and typhus fever was made with a fair degree of facility by local physicians.

The deaths from malarial fevers under various names, including bilious fever, present problems of greater difficulty in this connection. From the early medical literature of Baltimore, it is clear that bilious fever, or bilious remittent fever as it was usually called, was regarded by the medical profession as a form of malaria due to marsh effluvia and as synonymous with remittent malarial fever. It was commonly confused with yellow fever, which was regarded by many of the ablest physicians not as a separate disease but as a severe type of bilious remittent fever. To it was ascribed a very heavy mortality from 1812, when my records begin, until 1842. In 1851, bilious fever declined to 22.53 per 100,000, but during the next three years there was a distinct rise, succeeded by a considerable fall in 1856. By 1861, the rate per 100,000 had fallen to 15. After 1867, there was another rise, culminating in 1874.

If the rates for all the malarial diseases taken together were added to those for typhoid fever, the curve for the latter would show two distinct upward waves; one a very high short one, corresponding to the one evident on the graph between 1851 and 1856; the other a long wave, culminating in a very high peak in 1873. After 1874, the shape of the curve would not vary materially from that of typhoid fever as shown on the graph.

To remittent fever were ascribed comparatively few deaths before 1870, and the highest rate attained by this disease from 1851 to 1870 was 4.88 per 100,000. Intermittent fever was recognized as a separate disease from the beginning of my records for Baltimore. This disease ran a very irregular course, never reaching a very high mortality rate except in 1821 when the rate was 29.85 per 100,000, and, on the whole, its curve rises and falls with that of bilious fever. If all the deaths ascribed annually to intermittent fever were regarded as due to typhoid fever, the rate of the latter, from 1851 to 1866, would not be greatly altered, and its curve would be scarcely affected. Of all the varieties of malarial fever, this one is least likely to be mistaken for typhoid fever. From 1867 to 1874, inclusive, the rate for intermittent fever, and correspondingly the rate for all the fevers ascribed to malaria showed a decided rise.

In the above comparison, it is sought to bring out the facts that, if all the deaths ascribed to the different types of malaria, occurring between 1851 and 1874, inclusive, were classified under typhoid fever, the course of the curve for the latter would be changed in two respects; namely, the upward wave between 1851 and 1856 would be much higher, and the rise in the rates between 1861 and 1870 would have begun

several years earlier and continued three years longer—denoting two epidemic waves of typhoid fever instead of one, the peak of the first in 1853 and that of the second in 1871. In reality, however, as the malarial fever deaths between 1866 and 1874 were ascribed chiefly to those types of the disease least likely to be confused with typhoid fever (intermittent and congestive fevers), the confusion of malaria with typhoid fever as a cause of death could not very materially have affected the curve as plotted from the deaths officially ascribed to typhoid fever. Nevertheless, two points are evident: First, that typhoid fever before 1851 was hidden, mainly at least, in this particular group of diseases; and second, that, after its emergence as a distinct disease from the mass of other diseases characterized by continued fever, it was for a long time confused with them to such a degree that the mortality rate for typhoid fever obtained from the official figures is probably much lower than the true rate until about 1890.

It is very possible that typhoid fever was not infrequently confused with dysentery and diarrhea and with "inflammation of the bowels." As late as the first half of the 19th century, dysentery was thought by many physicians to be a form of malaria, with which it, in common with many other diseases, was so often complicated. Few of the population, in certain sections of the City at least, escaped malarial fever at this time. It is not unlikely, therefore, that cases of atypical dysentery, especially when complicated with malaria, were mistaken for typhoid fever. "Inflammation of the bowels," from 1840 to 1897, and diarrhoea, from 1875 to 1900, were credited with a considerable number of deaths, and it is probable that these two more or less indefinite affections were confused with typhoid fever. Just to what degree the confusion with typhoid fever of deaths classified under these three categories affected the typhoid rate, it is impossible to determine.

On the other hand, it would be grossly erroneous to assume that all the deaths officially ascribed to typhoid were actually due to this disease. There are ample reasons for concluding that many deaths from pneumonia, pleurisy, empyema, influenza, appendicitis, suppurative processes of the liver and the biliary and urinary tracts, acute miliary tuberculosis, acute phthisis, and the various cryptogenic suppurative infections, as well as pyæmia and septicæmia, following wounds and injuries, including those caused by surgical procedures—the large group of affections often characterized by the "typhoid state"—were attributed to typhoid fever. Before the isolation of para-typhoid fever as a distinct disease, deaths from this affection were probably classed under typhoid fever, as they are even now under the international classification of causes of death.

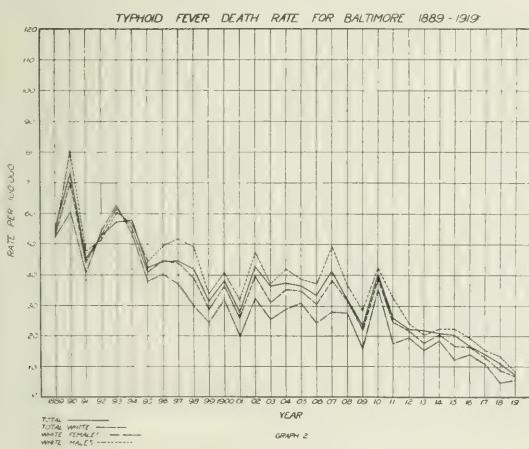
Another source of error to be taken into consideration is the influence upon the death rate of typhoid fever of deaths of non-residents, particularly those occurring among cases brought to hospitals in Baltimore for treatment. No separate account of these was kept until 1917. In the three year period, 1917 to 1919, these deaths accounted for 20 per cent of the total deaths from typhoid fever in the City. The deaths

within the City of non-residents from other States more than counterbalance the few deaths from typhoid fever in Baltimoreans away from home. It is probably warrantable to assume that this source of error was of relatively small importance until transportation was made easier by improved roads and the use of the automobile from about 1905. Since this period, probably from 15 to 20 per cent of the deaths recorded from typhoid fever in Baltimore occurred among cases imported from rural Maryland for treatment. As early as 1890, the Baltimore hospitals received many cases of typhoid fever from Sparrows Point, and it must be recalled that certain thickly settled parts of the adjacent suburbs, Highlandtown for instance, were readily accessible to some of the hospitals as many parts of the City.

From all the evidence at hand, therefore, it seems probable that the *shape* of the true mortality curve for typhoid fever for Baltimore, between 1851 and 1919, if we had the data for calculating it, would at least closely approximate that derived from the official figures, although the rates would be much higher in the earlier years.

*White Population.*—Graph 2 shows that the total rate for the white population exceeds the rate for the whole population only in 1893 and 1896. It closely approximates it in 1897, 1908, 1910, and 1916.

The rate for white females is well under the rate for the males, as well as under that for the total population, but it

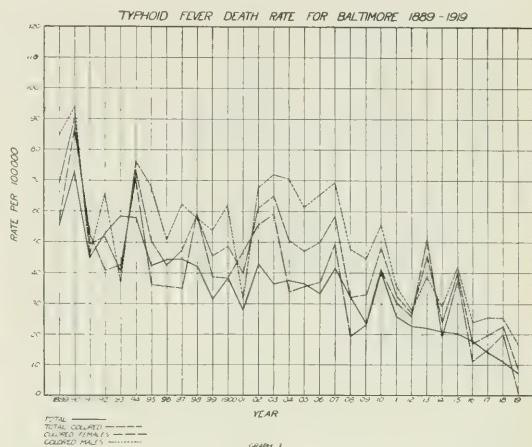


exceeds the rate for the total population in 1893. In general, the rate for the females follows accurately the rise and fall in the other rates, particularly the rate for total white and total population. In some few years, it falls or rises more abruptly than the other rates.

The rate for white males alone is uniformly higher than the other rates, with the following exceptions; in 1892, when it is slightly lower than the rest, and in 1894 and 1913, when it is slightly lower than the rate for the total population. This

rate rises and falls uniformly with the other rates and the curves approximately fit each other.

*Colored Population.*—The curves for the colored population in Graph 3 are much more complicated than those for the white. That for total colored falls considerably below

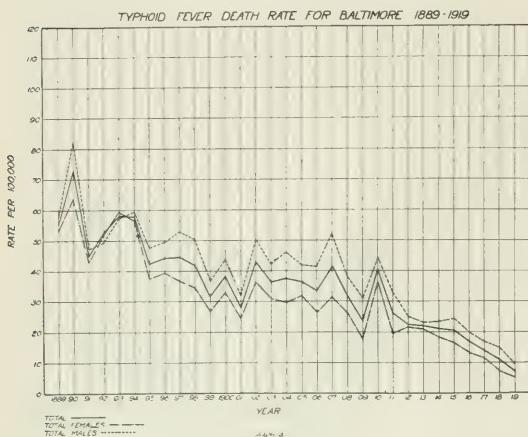


the total rate in 1893, the year in which the rate for the total white population was above the total rate. The course of the curve for the total colored population in relation to that for the total rate is in the main quite different, in that it often fails to follow the dips and elevations in the total rate, but even when it does follow these, it is apt not to conform closely. In 1913, the year in which the total white rate dips considerably below the rate for the total population, the total colored rate, on the contrary, shows a marked peak. In 1914, when there is but a very small fall in the total rate, there is a considerable drop in the total colored rate. In 1915, this is compensated for by a considerable peak in the colored rate. In 1916, the colored rate falls slightly below the rate for the total population. In 1917 and 1918, there is again a decided rise in the total colored rate, with a marked drop in 1919. The highest rate for the whole series of years is the colored rate for 1890 which reaches 90.13 per 100,000 while the highest rate for total whites is 69.93 per 100,000 in the same year. As would be expected from the different proportions which they hold in the population, the curve for the negro rate is nothing like so uniform as that for the white rate.

The rate for colored males is uniformly higher than that for colored females, except in 1893, 1901, and 1913, when the latter is markedly higher. The peaks and depressions of the two curves for colored males and females generally follow each other. There are, however, some notable exceptions.

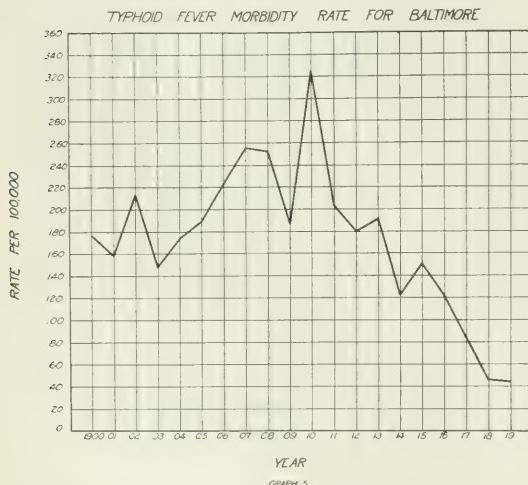
The curve for female colored is very irregular, but in general, it is higher than that for the total population. It is lower than the latter in 1895, 1896, 1897, 1904, 1908, 1909, 1914, 1916, and 1919. In some of these years, it is very noticeably lower.

*Males and Females.*—There is remarkable uniformity in the three curves plotted on Graph 4 which fit much more closely throughout than the curves previously considered.



The rate for females is slightly higher than that for both the total population and for total males in 1893, but with this exception, it is uniformly lower, and generally considerably lower than the rate for males. The rates for the two sexes vary as much as 20 per 100,000.

These graphs show very clearly throughout the period under consideration, from 1889 to 1919, inclusive, that the total rate



has been markedly influenced by both sex and color, that the presence of negroes tends to raise the general rate, and that the presence of females tends to lower it. In other words,

since the rates for the colored population are much higher than those for the white, and the rates for females of both races are lower than those for males, the total rate is influenced favorably by a low proportion of negroes and a high proportion of females in the population.

## II. MORBIDITY

Although typhoid fever was by law made reportable in 1894, it was not until 1900 that the cases were reported with reasonable accuracy. In Graph 5 are given the morbidity rates per 100,000 inhabitants from 1900 to 1919, inclusive. It will be noted that the morbidity curve corresponds in a general way with the mortality curve throughout its course, and that from 1910 to 1919 the two curves fit with a fair degree of accuracy. Unfortunately, data for comparing the morbidity in the colored and the white races are at hand for only 1918 and 1919. Comparison for these two years by sex and color is shown in Table 8. It will be noted that the morbidity rate

TABLE 8  
TYPHOID MORBIDITY RATES PER 100,000 BY RACE AND SEX  
FOR 1918 AND 1919

Year	Baltimore						Rural Maryland			
	White males	White females	Total white	Colored males	Colored females	Total colored	Total white	Total colored	Total morbidity	
1918.....	61.32	33.71	47.05	29.44	47.51	39.11	45.82	.....	.....	.....
1919.....	50.89	41.09	45.83	41.34	25.23	35.62	43.79	.....	.....	.....
Average for 1918 and 1919.	56.10	37.40	46.44	35.39	36.37	37.37	44.81	152.24	202.88	172.85

for the colored is decidedly lower than that for the white population, just the opposite to that which obtains for rural Maryland, as is shown by the figures calculated from data kindly furnished me by Dr. John S. Fulton, Secretary of the State Board of Health. The difference in the ratio of incidence of the disease in the two races in Baltimore as compared with rural Maryland is, to some extent, explained by the larger proportion of imported cases and of out of town infections among the white population in Baltimore. So far as may be judged by the figures for these two years, the incidence of the disease is not only greater in the white race than in the colored, but is greatest in white males, and greater in white females than in either colored males or females.

## III. CASE FATALITY RATE

Much interest attaches to the case fatality rate of typhoid fever in Baltimore, among other reasons because it has been used as a measure in estimating the degree of completeness of case reporting. Any conclusion in regard to case fatality must depend upon the accuracy with which cases and deaths are reported.

In his early studies on typhoid fever, Dr. C. Hampson Jones expressed the opinion, based upon the assumption that 10 per

cent is a normal average case fatality in this disease; that the number of reported cases fell far short of the actual number existing—in some years by nearly 70 per cent. That the reporting has not been perfect is beyond question.

There are several fallacies not uncommon in studies of this character which should be pointed out. In the first place, it is difficult to collect the information on which to set a correct standard for the case fatality rate for any disease, and this is especially difficult for typhoid fever. One must have a large number of cases in which the diagnosis is established with accuracy by the use of refined laboratory methods, and the chance of burying under typhoid fever individuals dead of other diseases must be eliminated by submitting to autopsy all the fatal cases in the series. An important source of possible error in Baltimore is due to the fact that many of the deaths registered as due to typhoid fever occur, as has already been pointed out, among cases brought from the counties of Maryland for treatment in the city hospitals, the reported cases being credited to the place of origin by the State Board of Health and the deaths then being recorded against Baltimore; *i. e.*, cases are transferred, but the deaths are not. The error lies in the fact that the divisor is disproportionately small. It is obvious, therefore, that for the purpose of establishing even an approximately correct case fatality rate, these two groups of cases and deaths must be reckoned, either combined or separately; *i. e.*, the county cases must be added to the divisor or the deaths among them must be subtracted from the dividend. The importance of this is well illustrated in Table 9, from which it will be seen that the average case

and deaths occurring among Baltimoreans in Baltimore is 15.01 per cent. From Sections I, II, and IV of this Table, it is clear that the official annual and average annual case fatality rates for 1917, 1918, and 1919 (for the old twenty-four wards, as shown in Section I) are far from the correct rates. The source of error, of course, in Section I lies in the smallness of the divisor, from which is officially excluded the number of cases from rural Maryland, in proportion to the dividend in which the deaths occurring among these cases are included. In Section II, this error is removed by adding the cases in question to the divisor. Section IV gives the corrected rates for Baltimore based on actual cases and deaths reported, but excluding from the dividend the deaths occurring among the cases charged officially against rural Maryland. In Section III are given the correct rates for the cases from rural Maryland treated in Baltimore during the years in question. It will be noted that the average annual case fatality rates for Sections III and IV (*i. e.*, rural Maryland and Baltimore) are approximately the same.

It is evident that the annual case fatality rates derived from the deaths and reported cases officially charged against Baltimore are not the true rates. The method of deriving annual case fatality rates by dividing the number of cases in a given calendar year is open to an error which may be considerable; not all the deaths that may occur among the cases reported in a given calendar year take place within that period of time. The early months of the calendar year will usually have deaths occurring among cases reported during the late months of the previous year,

TABLE 9  
CASE FATALITY RATES

Year	I		II		III		IV	
	Baltimore cases	Baltimore and rural Maryland deaths	Baltimore and rural Maryland total cases and deaths	Cases	Deaths	Rural Maryland	Cases	Deaths
	Percentage case fatality	Percentage case fatality	Percentage case fatality	Percentage case fatality	Percentage case fatality	Percentage case fatality	Percentage case fatality	Percentage case fatality
1917.....	544	12	16.91	696	92	13.22	152	24
1918.....	302	73	24.17	396	73	18.43	94	14
1919.....	293	49	16.72	327	40	14.8	84	5
Total and average.	1139	214	18.79	1419	214	15.08	280	43

I. Official figures and case fatality rates.

II. Official figures and case fatality rates as corrected by addition of cases from rural Maryland.

III. Figures and rates for rural Maryland cases treated in Baltimore, and deaths among such cases.

IV. Correct figures and case fatality rates for cases and deaths properly chargeable against Baltimore.

fatality rate for the three years, 1917 to 1919, inclusive, calculated without making this allowance, is 18.79, per cent, while a much lower rate is obtained either by adding the total cases reported from rural Maryland to the divisor, or by subtracting the deaths among them from the dividend. It will be noted that the average for the three years for the cases

TABLE 10  
CASE FATALITY RATES, ACCORDING TO SEX AND COLOR, 1919

Baltimore, 1919, twenty-four wards			
	Mortality	Morbidity	Percentage case fatality
Total white.....	35	259	13.89
Total colored.....	9	34	26.47
Total males.....	27	159	16.98
Total females.....	17	134	12.68
Male white.....	20	139	14.38
Female white.....	15	120	12.50
Male colored.....	7	20	35.00
Female colored.....	2	14	14.28
Total white and colored.....	44	293	15.01

and this process may be expected to continue throughout the series of years under consideration, and the last year in the series will almost surely lack some deaths. This error may be reduced to some degree by averaging the rates for a series of years.

A more accurate method is to take into account only the deaths occurring within the group of cases allowing a reasonable length of time for all the fatalities likely to happen within the group. This was done for the cases reported within the

old twenty-four wards during 1919. In the 293 such cases there occurred 44 deaths—41 during 1919 and 3 between January 1 and May 1, 1920. The case fatality rate thus derived, 15.01 per cent, happens to be the same for this single year as that for the average for the three years, as calculated by the usual method.

The accurate data for determining the influence of sex and color upon the typhoid case fatality rate in Baltimore are rather meagre, being limited to the year 1919. These are set forth in Table 10. On account of the smallness of the figures for some of the categories and the absence of correction for age, some of the percentages are perhaps subject to considerable probable error. Taking them at their face value, however, the risk rate of dying of clinically recognized typhoid fever is twice as great for colored as for white, somewhat greater for white males than for white females, and twice as great for colored males as for colored females, and nearly a fourth greater for total males than for total females.

#### SUMMARY OF THE KNOWLEDGE OF THE INFLUENCE OF DIFFERENT FACTORS ON TYPHOID FEVER IN BALTIMORE

From the mass of facts set forth in the preceding pages, it is evident that most of the various factors concerned in the spread of typhoid fever have acted continuously, but with varying degrees of force, during the whole period. The most important of these factors are:

- (1) Water Supply.
- (2) Crude Methods of Sewerage Disposal.
- (3) Milk.
- (4) Importation of cases and carriers in:
  - a. Immigrants.
  - b. Military.
  - c. Isolated Individuals.
- (5) Infection contracted without the City.
- (6) Associative Contact with Recent Cases and with Remote Cases; *i. e.*, Carriers.
- (7) Flies.
- (8) Bathing in Polluted Waters.

**Water Supply.**—The water supply was seriously polluted from the earliest times until 1911, but the degree of pollution has varied at different periods and with the sources from which the water was obtained. In 1850, at least a half and probably two-thirds of the drinking water was obtained from wells within the City. The proportion obtained from these sources was notably reduced after the City took over the water supply from the private company and provided a more abundant and better distributed supply after the establishment of the Lake Roland Dam on Jones' Falls in 1862. Nevertheless, a large part of the inhabitants clung to the internal water supply from springs and wells until long after this date. Through the efforts of the Health Department, these were practically eliminated in the old City of that period by the time of the annexation in 1888. It is probable that the Lake Roland watershed became heavily infected with typhoid fever during the Civil War. The completion of the Gunpowder

water supply system, with its numerous storage reservoirs, and the substitution to a very great extent of water from this source for the old Lake Roland water supply must have favorably influenced the course of typhoid fever for a considerable period after 1881. Indeed, with the exception of a few years after the annexation of 1888, the whole trend of the typhoid fever curve was distinctly downward for the next twenty years. After 1901, the water supply again became more and more polluted, and there was an upward wave in the typhoid fever curve until chlorination of the water supply was introduced in 1911, after which there was a distinct drop. As has been pointed out, the water supply was never obtained from a single source until 1915. The advantages which should have accrued from the various changes in the water supply were never wholly reaped because the old conditions were but slowly replaced, the older and poorer supplies being never entirely abandoned. For instance, after the introduction of the Lake Roland supply, a large proportion of the population still clung to the old springs and wells, and after many of these were abandoned in the old City in consequence of the activities of the Health Department, new sections which derived their water supply entirely from springs and wells were taken into the City; then too, after the introduction of the Gunpowder water supply, the old Lake Roland water supply was still to a great degree mixed with it. There is reason to think that the Lake Roland water supply obtained from Jones' Falls had become seriously polluted before the greater number of wells and springs were closed and this water was substituted. While it probably prevented a marked increase in the death rate, it exerted no great influence on its actual reduction from its previous level. It would appear that an infected external was substituted for an infected internal water supply.

**Sewerage.**—It has been shown that until 1915, with the exception of a few private sewers leading by the streams into the Basin and Harbor, human excreta containing typhoid bacilli from the cases and carriers emitting them were deposited in or on the ground. Had all the water supply been extra-urban and had all the dejecta gone into the soil, amateur hygienists to the contrary notwithstanding, there could be no serious objections to this method on sanitary grounds. But the water supply, until a late date, was largely of intra-urban origin, and the City was very closely built up. However, the spaces intended for drainage in many if not most cesspools became stopped, and the latter in consequence took on the attributes of surface privies. At one time it was the fashion to build water-tight cesspools, and the contents of many of these overflowed into streets, alleys, courts, and cellars. Material from many of the cesspools and privies, therefore, reached the wells and springs from the surface as well as through the soil. This material from overflowing cesspools and privies, as well as from the night-soil dumps, scows, and carts, was readily accessible to flies, the breeding and feeding of which in swarms were favored by the conditions of the stables, the imperfect surface drainage, and the inefficient collection and disposal of garbage. The methods of disposal of human waste favored,

to a high degree, the spread of typhoid fever by water, flies, and by milk and other foods. With the development and the perfection of the extra-urban and the gradual abandonment of the intra-urban water supply, the cesspool and the surface privy lost much of their importance as sources of typhoid infection. It is evident, that if the wells and springs had been abandoned sooner, the privy and the cesspool, though still harberors, would early have lost in importance as distributors of typhoid infection. After 1890, infection from this source was practically confined to that conveyed by means of flies. It is clear, therefore, that so far as concerns action other than from sources of infection for intra-urban drinking water, and the milk, and perhaps other foods, the sewerage remained a rather constant and relatively unimportant factor in the spread of typhoid until the new system was brought into general use in 1915. After 1915, it was possible for the sewerage system to exert in this direction but comparatively little influence on typhoid fever.

*Milk.*—During the whole period between 1851 and 1894, conditions were most favorable for the spread of typhoid fever by means of milk. In the first place, much of it was from cows kept within the City or nearby suburbs, where every chance existed for its pollution from actual cases of typhoid fever and from carriers. It was heavily watered, for much of the time with water from polluted wells and springs. It is not improbable that the substitution of less polluted water for watering milk before 1894 and the interference by the Health Department with watering after this date affected the typhoid death rate favorably. Under the laws of 1896 and 1902, the Health Department was able to improve very markedly the conditions under which milk was produced and sold within the City and thus to cut down very materially the opportunities for the dissemination of typhoid fever by milk produced and infected within the City. Under these laws, the urban cow was to a great extent but not entirely driven out. While these laws did not forbid the keeping of dairy cows within the City, they made it impossible to keep them within the closely built up sections and, on the whole, unprofitable, on account of the expense of constructing stables of the type required to keep them at all except in certain outlying districts. A great revolution in the control of the milk supply followed the enforcement of the milk ordinance of 1908, and by 1912 considerable oversight and control had been gained by the Health Department over the milk supply on dairy farms as well as within the City itself. Still between 1912 and 1918, numerous larger and smaller milk outbreaks were traced by the Health Department. As late as 1917, nearly 8 per cent of the reported cases were traced to milk in readily recognizable outbreaks. Besides these, there must have been large numbers of isolated or small groups of cases, in which the infection was carried by milk and which the machinery of the Department was inadequate to detect. The regulations of the Health Department could not, of course, prevent the removal of empty milk bottles from households with typhoid fever patients until such cases had been reported, and under the most favorable conditions two or three weeks pass between the beginning

of the illness and the report of the case. Unless milk bottles are uniformly sterilized as a matter of routine, bottled milk may be, during the prevalence of typhoid, more dangerous than milk served from the old-fashioned churn. When milk is sold from the churn or can, the purchaser receives it in his own container, and the dairy takes nothing infected away from the householder. The compulsory sale of milk in bottles without adequate provision for the cleaning and sterilization of the latter is a sanitary reform of doubtful value from certain standpoints. Until 1918, the refrigeration of the milk supply, whether in churns, cans, or bottles, was, with certain notable exceptions, quite inadequate, and in warm weather conditions were favorable for the multiplication of typhoid bacilli that reached milk.

It is only since the enforcement of the milk ordinance of 1917 that there has been reasonable security against milk-borne (including ice cream) typhoid in Baltimore. This law requires not only pasteurization and refrigeration of the general milk supply, but the cleansing and sterilization of all milk utensils, including the farmers' cans. No cases of typhoid fever were traced to milk in 1918 and 1919. It must be borne in mind, however, that owing to the great diminution in the number of cases of the disease in rural Maryland, as well as within the City, the opportunities for the infection of milk have become correspondingly less.

*Importation of Cases and Carriers:* (a) *Immigrants.*—It is well established by the writings of Nathan Smith and Bartlett, that typhoid fever was prevalent in New England before 1826 and was well established there as the most common continued fever by 1842. Some years later, Bartlett showed that the disease was widely diffused throughout this country, south as well as west.

From 1800 to 1850, Baltimore grew very rapidly by immigration; the chief sources of immigration from abroad being England, Scotland, Ireland, and Germany. There was during this time, especially in the earlier years, a large immigration from New England and Pennsylvania, as well as from Virginia. In all of these places typhoid fever was then widely prevalent, and it is therefore certain that these immigrants as clinical cases and carriers contributed largely to the spread of the disease, doubtless long before strongly entrenched here. The later European immigrations were all from typhoid stricken countries. Baltimore's great prominence as a port city added to this danger. In the lower part of the City, where recent immigrants mostly settled or lodged, while transients, conditions were especially favorable for contamination of the wells and springs and for the spread of the infective agent by contact and by flies.

*Importation of Cases and Carriers:* (b) *Military.*—For the ten-year period before the Civil War, the average mortality rate for typhoid fever in Baltimore was about 45 per 100,000. From 47.09 in 1860 it jumped to 75.92 in 1861, remaining high during the whole war period and for some years afterwards. The highest portion of the typhoid mortality curve lies between 1861 and 1872. During the whole war, Baltimore and its vicinity were crowded with federal troops brought

from widely separated parts of the country and from the hospitals and battle-fields of Virginia, West Virginia, and probably Kentucky, and perhaps further south and west. The City became a great collecting and distributing point for troops. There were a number of military hospitals, some very large, for the treatment not only of the wounded, but of the sick. All the facts favor the inference that the presence in the City of great numbers of transient soldiers of an army known to be highly affected with typhoid fever must have resulted in an increase in the morbidity and mortality rates of this disease among the inhabitants. It is very probable that the soldiers were an important factor in spreading infection, not only through the wells and springs within the City, but over the Lake Roland watershed.

*Importation of Cases and Carriers:* (c) *Isolated Individuals.*—In addition to the large immigrations, attention should be called to the fact that large numbers of cases were annually brought into the City for hospital treatment, and even of late years a not inconsiderable proportion of the typhoid fever cases and deaths have occurred among individuals, from other states and on foreign ships, who have arrived in the City with the disease.

It has been pointed out above that for the three years just past, 20 per cent of the total deaths of typhoid fever in Baltimore occurred among individuals brought in to Baltimore hospitals from rural Maryland for treatment. On the whole, it seems probable that the mortality rate for typhoid fever in Baltimore has been, throughout the history of this disease, materially influenced by the importation of isolated cases of the disease.

*Infection Contracted Without the City.*—As far back as 1890, it was recognized in the Health Department that a considerable proportion of the cases of typhoid fever reported in Baltimore was contracted without the city limits, either in rural Maryland or in other states. It has been shown that in 1919 over 12 per cent of the reported cases certainly received their infection outside of the City and that 8 per cent probably had this source of origin. Until the last few years, there is reason to think that many cases were infected at resorts on the Bay and the numerous small rivers and estuaries of the Bay, near the City, particularly at the so called "shores." When the great prevalence of typhoid fever, until recent years, in rural districts of Maryland and other states, which Baltimoreans visited for work or pleasure, is taken into consideration, it seems probable that in the past this source of infection was even more important than at present.

In this connection, it is significant that the morbidity rate for Baltimore has declined in parallel with that of rural Maryland, particularly in the counties adjacent to Baltimore, in which the greater proportion of infection took place, and that nearly all of the cases of typhoid fever, attributed to these sources of infection within the last few years, have occurred in the warm weather when typhoid fever is most prevalent in the country districts.

*Associative Contact with Recent Cases and with Remote Cases; i. e., Carriers.*—If 12½ per cent of the cases could be

traced to contact with recent cases in households and hospitals and nearly 8 per cent to contact with remote cases in households, *i. e., carriers*, in 1918 and 1919, it is reasonable to suppose that these factors exerted at least as great an influence upon the people in former years, since their conditions of life and their habits were much more favorable for infection by associative contact than at present.

*Flies.*—Enough has been said under other headings to indicate that until very recently the general sanitary conditions of the City were peculiarly adapted to fly-borne typhoid. It remains to be pointed out that, particularly in the crowded sections of the City and among foreigners, the great numbers of flies had ready access to the excreta of typhoid patients. The fly season is a long one, screening was almost unknown, and among certain elements in the population, the screening of the apartments of typhoid fever patients was enforced with great difficulty or not at all.

*Bathing in Polluted Waters.*—It is probable that until the last few years, this has been a frequent source of infection of typhoid fever within the city limits. It is not improbable that many persons were infected by bathing in the polluted streams within the city limits, as well as in the Basin and in the middle branch of the Patapsco at Spring Gardens.

#### UNEXPLAINED CASES

The question of the source of infection of the group of *unexplained cases* must be faced. Even if it be granted that the explanations offered for the *explained cases* are adequate—and the value of some of these (probable and possible out-of-town infections, infection from remote cases in which carriers were not demonstrated by culture methods, and neighborhood infection by flies) is acknowledged to be questionable—there still remains a large group of cases upon the origin of which no light has been thrown.

In the absence of some other obvious explanations, it is natural and usual to attribute these cases to water and milk-borne infection. But slight consideration shows this to be unsatisfactory, and the same question arises in all cities with comparatively low and falling typhoid fever rates, following the inauguration of apparently effective water supply and sewerage and milk protection systems. In the old twenty-four wards of Baltimore, the sewerage system—with the exception of certain districts which, however, do not show any particular difference in typhoid incidence—may be eliminated from consideration. If any dependence can be placed upon the value of the bacteriological examinations conducted independently in the laboratories of the filtration plant and of the Health Department during 1919, the city water supply in that year at least, according to the accepted and apparently logical standards, may be acquitted. The number of reported cases on the watershed were very few and were supervised both by the Water Department and by the very efficient deputy State Health Officer. If the water supply were responsible for some or even most of the cases now under consideration, it is reasonable to suppose that there should have been an even greater number than actually occurred.

To state that no cases were traced to milk is not equivalent to asserting that infection was not spread through this medium. It is unwarrantable to assume that all chances of the spread of the disease by milk were successfully guarded against. No one concerned with the oversight of the milk supply thinks that all the milk utensils were sterilized and that all the milk was adequately pasteurized. There is still a chance that some typhoid fever in Baltimore is spread by milk. However, if the milk supply was even an important source of infection for this group of cases, explanation would still be lacking for the comparatively large proportion of these cases in which the use of milk as a beverage was denied.

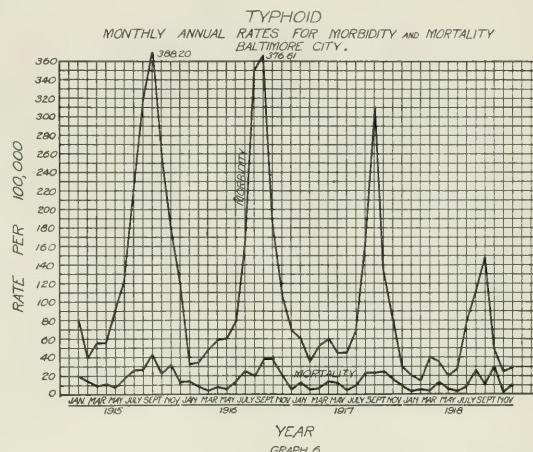
When this *unexplained* group is analyzed, it is found that the cases do not vary essentially from the *explained* group in age, sex, color, or seasonal and locality distribution. They vary in only one attribute.

It is certain that, in some cases at least, more complete histories could have been elicited. Some of the patients were not only illiterate and stupid, but many could not express themselves in languages familiar to the investigators. It must also be recalled that many of the patients were too ill at the time of the investigations to give clear answers and to recall all the details of their histories. In such cases, the investigators had to rely upon the testimony of relatives and friends. Again, it is not possible for an individual to recall all his actions and contacts some weeks after an event. After all, the modes of transmission inquired into and which we have been considering are only the very obvious and perhaps there are others quite as important.

There are in this community hundreds of survivors of clinically recognized and unrecognized attacks of typhoid fever who are potentially carriers and who from time to time may pass on the infective agent to others. A colored cook, proven to be a carrier responsible for 9 cases of typhoid fever among college girls and who appeared to be quite frank when submitted to the closest interrogation, was unable to recall a febrile illness suggestive of ordinary clinical typhoid fever. She described, however, very clearly the symptoms of an attack of acute cholecystitis which she had had about a year before. Her story was confirmed later, even as to dates, by her physician. She apparently had had an attack of primary cholecystitis due to *B. typhosus* and resulting in the carrier state. Had she not by chance transferred typhoid infection to a number of college girls at the same time, she would probably not have been apprehended. Upon such chances as these the transmission of this disease and the recognition of its mode often depend. None of this woman's personal associates gave a history of frank typhoid fever either before or after her attack of cholecystitis. The victim of typhoid fever rarely knows the typhoid fever history of his intimate associates outside of his family, and, when questioned, cannot tell whether any of his hosts or hostesses or their servants have had the disease. To find a hidden carrier, it would be necessary to take a census of the patient's known and unknown contacts. A large proportion of the several hundred food handlers whom I have had cultured with negative results may be intermittent carriers,

infecting from time to time people not intimately associated with them. There must be in this community a considerable number of so called "healthy carriers," typhoid carriers who have not developed clinical typhoid fever and who are effective infectors, or who may become self-infected; *i. e.*, their barriers of resistance may at some time become ineffective against typhoid bacilli on the surface of their bodies (on the mucose of the biliary, intestinal, or urinary tracts). It is impossible to set a time limit between the beginning of the healthy carrier state and true infection.

If butter and certain kinds of cheese were exhaustively studied, with more refined methods than now exist for isolating *B. typhosus*, it is probable that it would be found that



these foods are a not uncommon means for the transmission of typhoid fever in urban communities.

Now that the City Fathers, after many years of fumbling, have finally made those general sanitary provisions necessary for the reduction of the incidence of typhoid fever to a comparatively low level, in the old twenty-four wards, and the obvious may be set to one side, the public health administrator of an inquiring turn of mind may turn himself to the much more interesting and important problem of determining the less obvious or hidden means of transmission of the disease.

#### SEASONAL DISTRIBUTION

It has long been held that typhoid fever in Baltimore is essentially a disease of the summer and autumn. This has not always been the case, for during many years, from 1856 to 1881, the number of deaths in the winter months—December, January, and February—equalled or even exceeded those for the summer and fall months. It is interesting that this was the period during which so much of the water supply was intra-urban in origin and when the extra-urban supply was entirely or mainly derived from Jones' Falls. Since 1881, the highest monthly mortality has remained permanently in the summer and fall months. During this period, the springs

and wells in the City as a whole were abandoned and the Gunpowder water supply was largely or entirely substituted. As long as the water supply was grossly and steadily polluted, the distribution of the disease tended to be more evenly distributed throughout the year.

A study of the reported cases since 1900 shows that from February, the month of lowest incidence, there is a very gradual progression of the disease until July when there is a rapid rise, culminating in a peak usually about the middle of September and more rarely late in August, or even early in October. The decline is usually somewhat abrupt during September or October and more gradual in November, December, and January. The deaths follow the same general course, lagging about one month behind the reported cases. This course of the disease is well shown on Graph 6, on which the monthly annual morbidity and mortality rates are given for the years 1915 to 1918, inclusive.

Analysis of the modes of action of the factors influencing the incidence of typhoid fever in Baltimore makes clear why, during the second period, the greatest incidence and mortality should be in the warm months. This is the season when the greatest number of imported cases occur, when conditions are most favorable for infection by means of milk, milk products, and other foods (and in which consequently most of the observed milk epidemics have occurred), when there are the greatest number of cases upon the watersheds, and when conditions are auspicious for the dissemination of the infective

agent by carriers, clinical cases, flies, and bathing in polluted waters.

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## THE VALUE OF THE WASSERMANN REACTION IN OBSTETRICS, BASED UPON THE STUDY OF 4547 CONSECUTIVE CASES\*

By J. WHITRIDGE WILLIAMS

I have always been interested in the relations between syphilis and obstetrics. This interest originated in connection with the microscopic examination of the placenta, which has been a routine procedure since the beginning of our service, with the result that we have now available the records of some twenty thousand such examinations. That study soon taught me that lesions frequently occur in the placenta which are characteristic of syphilis, and which enable one to detect the disease in many cases in which its existence is otherwise unsuspected.

When the Wassermann reaction was first described, I welcomed it as an additional aid in diagnosis, and immediately began to compare the results obtained by its means with those following the microscopic examination of the placenta. For a number of years, however, I employed it only when something in the history of the patient suggested the possible existence of syphilis. Although my investigations had shown that syphilis was a frequent complication of pregnancy and was one of the common causes of foetal death, I did not appreciate its full significance in obstetrical work until 1915. At that time I studied the foetal and infantile deaths in a series of 10,000 consecutive deliveries, and in my presidential

address before the American Association for the Prevention of Infantile Mortality, I stated that syphilis was the most important single cause and constituted the etiological factor in 26 per cent of the deaths occurring in my service between the end of the seventh month of pregnancy and the two weeks immediately following delivery.

As the result of that study, I concluded that the most immediately fruitful field for prenatal work lay in the earliest possible recognition of the existence of syphilis and its intensive treatment during pregnancy, and that this could best be accomplished by making a Wassermann test upon every patient entering the service. Consequently, from April, 1916, to the present time the routine procedure is to withdraw a specimen of blood from every patient at her first visit to the dispensary and, if a positive Wassermann is obtained, to subject her to intensive treatment in the syphilitic department of the hospital. Furthermore, in the hope of increasing our knowledge concerning the incidence of the disease, as well as its clinical significance for the mother and child, a Wassermann is likewise made from a sample of foetal blood obtained from the umbilical cord immediately after delivery. Likewise, every placenta is weighed and described macroscopically, after which portions of it are hardened, cut, stained and subjected to microscopic examination. Finally, whenever the

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child is born dead or dies within the first two weeks of the puerperium, every effort is made to secure an autopsy, at which particular attention is paid to the detection of syphilitic lesions, and a positive anatomical diagnosis is not made unless spirochetes can be demonstrated in the foetal organs.

The present work is based upon the study along these lines of four thousand women and their children who were delivered in the service, out of 4547 admissions, between April, 1916, and December 31, 1919. The patients were almost equally divided between whites and blacks, though the latter slightly predominated—1839 and 2161, respectively.

On this occasion I shall refer incidentally to the part played by syphilis in the causation of foetal death, then I shall consider more fully the significance of the maternal and foetal Wassermann, after that I shall consider briefly the value of the microscopic examination of the placenta in the detection of syphilis, and finally say a few words concerning the status of Colles' law.

I am able to make the remarks concerning syphilis as a cause of foetal death comparatively brief, for the reason that the subject was considered in detail in my article on "The Significance of Syphilis in Prenatal Care and in the Causation of Foetal Death," which appeared in the BULLETIN of The Johns Hopkins Hospital, May, 1920.

That article was based upon the study of 302 foetal deaths—99 whites and 203 blacks—which occurred in the 4000 deliveries under consideration. It showed that syphilis was the most important single cause of death, and that it was responsible for 34.4 per cent of the total number. These figures did not include the children discharged alive with hereditary syphilis, nor those in whom the disease developed later. Furthermore, it was shown that syphilis was responsible for more than twice as many deaths as the next most important cause, namely dystocia, as well as for nearly as many deaths as the next three most common causes combined, namely dystocia, toxæmia and prematurity. My figures indicated that these three causes were responsible for 37 per cent of the deaths as compared with 34.4 per cent for syphilis. At the same time, I pointed out the great difference in the incidence of the disease in the two races; syphilis being responsible for 12 of the 99 white, as contrasted with 92 of the 203 black deaths, an incidence of 1 to 8, and 1 to 2, respectively.

After these preliminary remarks, I shall pass on to the study of the significance of the Wassermann reaction in pregnant women. In the 4000 women delivered during the period under consideration, 449, or 11.2 per cent, presented a positive reaction during pregnancy. Its incidence was much greater in the black than in the white women, being 16.29 per cent and 2.48 per cent, respectively. In other words a positive Wassermann was noted in every sixth colored woman, as compared with every forty-fifth white woman.

It is comparatively easy to collect such gross figures, but when we attempt to determine their significance, we immediately fall into very great difficulty, as we are brought face to face with a number of conditions which we cannot at present satisfactorily explain.

Chart I gives an idea of the complexity of the problem. The 449 cases included in it are arranged in three great groups, according as the patients were not treated at all, were treated imperfectly, or were well treated prior to delivery. In each group there are a number of subdivisions, amounting to 24 in all, which indicate as far as possible the condition of the child, the microscopical findings in the placenta and the results at autopsy. By way of explanation, it may be said that the treatment was regarded as efficient only when the patient had been given a course of five or six injections of salvarsan followed by mercurial treatment, which resulted in the permanent disappearance of the positive Wassermann. Under inefficient treatment were included such patients as had received one or more injections of salvarsan, but in whom, for one reason or another, the course of treatment had not been completed; while, of course, no explanation is required for the patients who received no treatment, except in so far as failure to give it is concerned. In most cases in this category lack of treatment was due to the fact that the women were registered late in pregnancy, and fell in labor before it could be instituted; while occasionally it was due to the fact that the patients did not return for treatment after having been directed to do so.

With these figures before us, it may be asked, What is the significance of a positive Wassermann reaction occurring in a pregnant woman? Does it inevitably mean that she has syphilis, and will she transmit the disease to the child? To the first question, I am not prepared to give a conclusive answer, although I shall have more to say concerning it in the section devoted to Colles' law; but concerning the second question, our observations permit a definite statement to the effect that the existence of a positive Wassermann on the part of the mother does not necessarily mean that her child will develop syphilis.

This is clearly demonstrated by the consideration of the untreated cases included in Chart I. Our figures show that 87 of the 169 children concerned (A and C), or 51.5 per cent, were discharged in good condition, or were born dead or died during the puerperium, but presented no signs of syphilis at autopsy. Moreover, in all of the 87 cases the microscopic examination of the placenta was negative. On the other hand, 57 children presented either clinical or anatomical evidences of syphilis (B, E, G and I). In 19 other cases the placenta was syphilitic, and thus raised the presumption that the child was likewise suffering from the disease. Closer study, however, shows that such is not inevitably the case; as in four instances (H) the children were discharged in good condition, while in two others (J) they died, but showed no signs of syphilis at autopsy. In 13 cases (D) the children died, but did not come to autopsy, so that a positive statement as to the cause of death cannot be made, although the presumption is that it was due to syphilis. Finally, in six other cases (F) the placenta was normal, but the dead children were not autopsied. In this group, likewise, a positive answer cannot be given, although the presumption is that syphilis was not the cause of death. In other words, of the children born to 169 women

presenting a positive Wassermann during pregnancy, but who were not subjected to treatment of any sort, 51.5 per cent showed no evidence of syphilis, 33.7 per cent had definite syphilis, while in 14.7 per cent the results were doubtful. Consequently, it appears conservative to assume that the evidence at our disposal indicates that less than one-half of such women, and possibly even a smaller number, will have syphilitic children.

Chart I also affords a striking demonstration of the beneficial effect upon the child of treatment administered to the mother during pregnancy. Thus, while 51.5 per cent of the children of the 169 women who were not treated showed no signs of syphilis, 66.8 per cent were free from the disease in the 102 women who were inefficiently treated, as contrasted with 93.6 per cent in the 178 women who were well treated. Or, to express it in another way, the incidence of syphilis was 48.5, 33.2, and 6.7 per cent in the three groups respectively. Such figures are extremely encouraging and might tempt one to conclude that ideal prenatal care might lead to the total abolition of syphilis in the child. Such a conclusion, however, is too roseate, and as the sequel will show is not justified.

Chart II gives a totally different aspect to the question. It is based upon the study of 109 other women in the series who presented a negative Wassermann during pregnancy, but in whose history some mention of syphilis was made. Roughly speaking, these women may be classified in four categories: (a) Those who had presented a positive Wassermann in a previous pregnancy, but who had been treated and apparently cured; (b) those in whom autopsy upon the child conclusively demonstrated the existence of syphilis; (c) those presenting a positive placenta and an apparently normal child; and (d) cases in which the paternal Wassermann was positive. Upon analyzing the cases included in this chart, we find that 44 women had been effectively treated in a previous pregnancy, and may be regarded as having been cured of syphilis, leaving 65 for consideration. These 65 women had 54 dead and 11 live children. Forty-three of the dead children came to autopsy and 11 did not; 40 of the former were definitely syphilitic, while 3 were not. Of the 11 children, which were not autopsied, 7 (D) had positive placentæ and presumably were syphilitic, while in 4 (F) the placenta was normal and the mother had been treated in a previous pregnancy. Of the 11 children which were born alive, 3 presented characteristic lesions of hereditary syphilis (I and L); while 8 were discharged in good condition (E, G, and O). Concerning the three cases in subdivision G, more will be said in the section dealing with Colles' law.

In other words, of the 65 children under consideration, 43 were definitely syphilitic; 11 others died, but were not autopsied; 3 gave negative results at autopsy; and 8 were discharged in good condition.

What does this mean? At first glance it would appear to invalidate almost entirely the value of the routine Wassermann in obstetrics, but a little further consideration indicates that so pessimistic a conclusion is not justified. All that we

can say positively is that 43 syphilitic children were born to 65 women who presented a negative Wassermann.

What this means serologically it is impossible to state at this time, but practically it means that in our material about one baby in 100 (43 out of 4000) will have syphilis even when the maternal Wassermann is negative, and consequently one is not justified in claiming that the most ideal prenatal care can entirely eradicate the disease as a cause of foetal death. Of course, in practice the results will not be quite so bad as here indicated, for the reason that the condition would probably be recognized after the birth of the first syphilitic child, when the mother would be properly treated with a reasonable prospect that future children would be exempt from the disease.

The practical bearing of this aspect of the problem may perhaps be elucidated by a little calculation. For example, if it is assumed that 11 per cent of our women have a positive Wassermann, and that without treatment one-half of their children would be syphilitic, we should expect 55 syphilitic children in every 1000, plus 10 others (1 per cent), which would be born of women with a negative Wassermann, or a total of 65 per 1000. Consequently, our figures indicate that even though routine Wassermann tests were made early upon all pregnant women and efficient treatment instituted at once, only five-sixths ideal results would be obtained. Of course this would apply only to the first delivery in the service, as in the women with negative Wassermanns the existence of syphilis would be detected after the birth of the first child, when treatment would be immediately instituted and be followed by excellent results in the future.

Generally speaking, I feel justified in concluding that such a result should not discourage us, for if we were able to reduce the foetal mortality from syphilis by five-sixths, its eventual incidence would scarcely exceed 1 per cent, and it would be converted from the most common cause of foetal death into an infrequent one.

Turning to the consideration of the significance of the foetal Wassermann at the time of delivery, our material shows that a positive result was obtained in 38 of the 4000 observations, approximately 1 per cent. This means that only a small fraction of the children born of mothers with a positive Wassermann present such a reaction. It should, however, be remembered that macerated children are not available for the test, as their blood is already "laked."

In order to arrive at a conclusion as to the value of such investigations, we have attempted to determine the fate of the 38 children concerned. For this purpose, they were visited at their homes, subjected to a careful physical examination, and a sample of blood was removed in order that the Wassermann might be repeated. As three years had elapsed since the oldest cases had been discharged, it is not surprising that nine of them could not be located, thus leaving 29 available for consideration. Fourteen of the children died within the first month, mostly in the service, and in 12 of them syphilis was demonstrated. Five of the surviving children developed clinical syphilis later, while 10 presented no clinical signs of

12½ inches →

## TOTAL NUMBER OF CASES (449).

- 169 CASES, NO TREATMENT.
- 6 No treatment, placenta and child normal.
  - 40 No treatment, placenta syphilis, child syphilis.
  - 18 No treatment, placenta normal, autopsy negative.
  - 12 No treatment, placenta syphilis, child dead, no autopsy.
  - 9 No treatment, placenta normal, autopsy syphilis.
  - 6 No treatment, placenta normal, child dead, no autopsy.
  - 4 No treatment, placenta normal, child clinical syphilis.
  - 4 No treatment, placenta syphilis, child living and well.
  - 2 No treatment, placenta syphilis, child clinical syphilis.

## 102 CASES, INEFFICIENT TREATMENT.

- 62 Treatment inefficient, placenta and child normal.
- 10 Treatment inefficient, placenta syphilis, autopsy syphilis.
- 9 Treatment inefficient, placenta syphilis, child dead, no autopsy.
- 6 Treatment inefficient, placenta normal, child clinical syphilis.
- 5 Treatment inefficient, placenta syphilis, autopsy negative.
- 4 Treatment inefficient, placenta normal, child dead, no autopsy.
- 3 Treatment inefficient, placenta normal, autopsy negative.
- 2 Treatment inefficient, placenta normal, child clinical syphilis.
- 1 Treatment inefficient, placenta syphilis, child living and well.

## 178 CASES, GOOD TREATMENT.

- 166 Treatment good, placenta normal, child normal.
- 6 Treatment good, Wass. still +, placenta normal, child normal.
- 3 Treatment good, placenta normal, child syphilis.
- 2 Treatment good, placenta syphilis, child normal.
- 1 Treatment good, placenta syphilis, child dead, no autopsy.



CHART I.—Graphic analysis of results in 449 women presenting a positive Wassermann (1/36 inch to case).

169 Patients with no treatment had 48.5% syphilitic children.

102 Patients with inefficient treatment had 39.2% syphilitic children.

179 Patients with efficient treatment had 6.7% syphilitic children.

## TOTAL NUMBER OF CASES (109).

- 44 Following treatment in previous pregnancy, placenta and child normal.
- 24 No treatment, placenta syphilis, autopsy syphilis.
- 19 No treatment, placenta normal, autopsy syphilis.
- 7 No treatment, placenta syphilis, child head, no autopsy.
- 4 No treatment, placenta syphilis, child normal.
- 4 Following treatment in previous preg., placenta normal, child dead, no autopsy.
- 3 Following positive Wass. without treatment, placenta and child normal.
- 2 No treatment, placenta syphilis, autopsy negative.
- 2 Treatment inefficient, placenta normal, autopsy syphilis.
- 2 Treatment in previous pregnancy, placenta syphilis, autopsy syphilis

- 1 No treatment, placenta syphilis, child clinically syphilis.
- 1 Paternal Wass. +, placenta syphilis, autopsy syphilis.
- 1 Paternal Wass. +, placenta normal, autopsy syphilis.
- 1 Treatment inefficient, placenta normal, child normal.
- 1 Treatment in previous pregnancy, placenta normal, autopsy negative.



CHART II.—Graphic analysis of 109 cases in which the maternal Wassermann was negative, but in which some mention of syphilis was made in the history (1/18 inch to case).

B 24	I 2	D 7	E 4	H 2
C 10	L 1	F 4	G 3	P 1
J 2			O 1	
K 2				
M 1				
N 1				
— 40	— 3	— 11	— 8	— 3 —
Positive autopsy	Clinical syphilis	Child dead no autopsy	Child normal	Autopsy negative

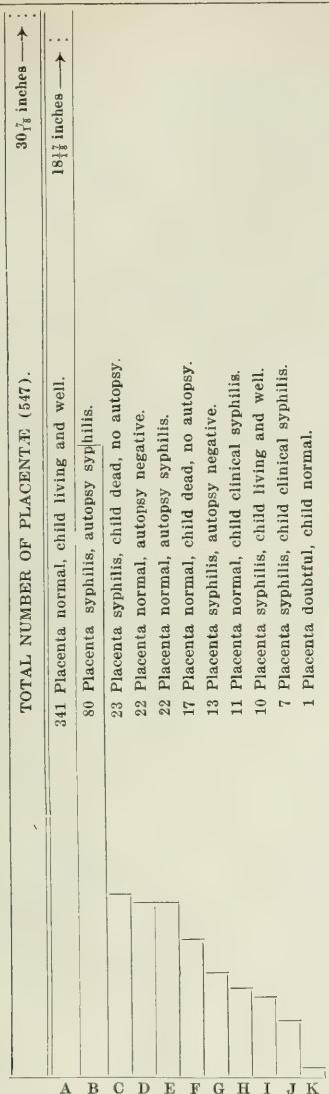


CHART III.—Graphic analysis of results of microscopic examination of 547 placentæ from patients included in Charts I and II (1/18 inch to case). The difference between 558 and 547 is due to the fact that the sections from 11 placentæ were lost, and consequently could not be verified.

the disease. In the latter a Wassermann repeated months or years after the original gave positive results in five children, while it was negative in the other five.

In other words, out of the 29 children who presented a positive Wassermann at birth, 17 developed definite evidences of syphilis, 5 showed no clinical signs, but continued to have a positive Wassermann, while 7 showed no signs in association with a negative Wassermann. Accepting the positive Wassermann as evidence of the existence of syphilis in the child, it appears that the primary reaction corresponded with the clinical and anatomical findings in 76 per cent of the cases.

At first glance these figures would seem to indicate that the foetal Wassermann is of considerable prognostic value, and indicates that the great majority of children presenting it either have syphilis or will develop it later. The validity of such a conclusion, however, is put in serious doubt when an attempt is made to trace what has happened to the children who presented a negative Wassermann at birth. I have attempted to follow up all the children who were discharged from the service in good condition in order to learn their subsequent history and to obtain a subsequent Wassermann. Unfortunately, this is often extremely difficult, as many of the mothers move away and give their neighbors no information concerning their new location, so that it is impossible to find them, except by accident. We have, however, examined a large number of such children, and among them have thus far found 10 whose Wassermann at birth was negative, but now is positive. In view of these findings, we are forced to the conclusion that a positive Wassermann at birth does not necessarily imply that it will remain so; and conversely, that a negative Wassermann at birth does not necessarily mean that it may not become positive later.

Upon analyzing our material from another point of view, we find upon deducting the children dying within the first month, as well as those who presented signs of clinical syphilis, that we have 10 left, none of whom developed clinical signs of the disease. In five of these the positive Wassermann persisted, while in the other five it had become negative. What will eventually happen to the first group can only be determined by subsequent study.

With these results before us, I feel that we are justified in concluding that the information obtained by the Wassermann made from the fetal blood at birth is not commensurate with the time consumed, nor the money expended in such investigations. That I am not alone in this opinion is shown by the study of Fildes, who in 1915 reported that he had found a positive Wassermann at the time of birth in 14 out of 1015 children—1.3 per cent. Prolonged observation showed that only one of them subsequently developed clinical syphilis. Seven of the others who were examined later presented a negative Wassermann; while in three other children the original negative Wassermann later became positive. Consequently, he felt justified in drawing conclusions identical with those indicated above.

During the course of years, I had become convinced from the routine microscopic study of the placenta that the syphilitic lesions occurring in it are extremely characteristic, and afford more conclusive evidence of the existence of syphilis than the demonstration of a positive maternal Wassermann, and in general tally fairly closely with the autopsy findings in the child. For this reason I was curious to ascertain in how far the results of the present study would sustain such conclusions.

Chart III gives a graphic picture of the relation between the microscopic findings in the placenta and the clinical and anatomical condition of the child based upon the study of 547 cases. The chart represents the combination of the 449 women presenting a positive Wassermann as shown in Chart I, and the 109 women presenting a negative Wassermann as shown in Chart II, and should include 558 cases. The difference between that figure and the one mentioned is due to the loss of 11 placental preparations. It may here be stated that in the preparation of the material upon which this study is based, the microscopic slides from every placenta concerned were reexamined for the purpose of verifying the diagnosis.

Upon referring to Chart I, we find that a positive Wassermann was originally obtained in 449 women, which later became negative in 172 out of the 178 women who had been efficiently treated, so that 277 cases are available for ascertaining in how far a positive maternal Wassermann corresponds with the existence of the so-called microscopic lesions of syphilis in the placenta, or with the presence of positive clinical symptoms or autopsy findings in the child. Upon analyzing our figures upon this point, we find that the two correspond in 109 instances (B, D, E, G, H, I, J, L, M, N, O, R and S), and fail to correspond in 158 instances (A, C, K, Q and U); while in 10 other instances (F and P), in which the placenta was normal but the dead child did not come to autopsy, no conclusion could be drawn. In other words, in this series the maternal Wasserman tallied with the placental or foetal findings in 39.35 per cent and failed to tally in 57 per cent of the cases, while in 3.6 per cent the conditions were such that a positive conclusion could not be reached.

It would consequently appear that since there are only four chances out of ten of the results corresponding, it is hazardous to attempt to draw any conclusion concerning the condition of the placenta or of the child from the existence of a positive maternal Wassermann during pregnancy.

Of course it may be objected that such a deduction is not justifiable because of the fact that 102 women who received imperfect treatment during pregnancy had been included in the series, and such an objection must be admitted. On the other hand, information not susceptible to such criticism may be obtained by restricting our inquiry to the 169 women who received no treatment of any kind. Upon deducting the six questionable cases, in subdivision F, we have 163 untreated cases, and of these 67 tallied and 96 failed to tally—42 and 58 per cent, respectively, or essentially the same incidence as before.

The problem may be approached in another way. Upon comparing the placental findings in Chart III with the condition of the children, and taking no account of the Wassermann reaction, it is noted that in 451 instances (A, B, D, J and K), the results tally, while in 56 instances (E, G, H and I), they do not. In addition there are 40 cases in groups C and F, in which the dead children did not come to autopsy, and consequently a positive statement could not be made as to their condition. In other words, in the 547 placentæ concerned, the results tallied in 82.5 per cent, while upon deducting the 40 questionable cases the figure becomes increased to 88.1 per cent.

Furthermore, we may attempt to solve the problem from still another point of view, and we can compare the degree of correspondence according as the placenta was normal or definitely syphilitic. In the 414 cases included in the former category, we note the following results: In 343 the child was discharged alive and well; in 22 it was dead born, but autopsy revealed no evidence of syphilis; while in 22 others autopsy showed that death was due to syphilis, and in 11 the live child presented characteristic lesions of clinical syphilis; while 17 dead children did not come to autopsy. Upon deducting the last 17 cases in which no statement concerning the cause of death is permissible, we find 397 normal placentæ associated with 364 non-syphilitic children. In other words, the results tally in 91.6 per cent. On the other hand, in the 133 cases in which the placenta was definitely syphilitic our figures show 80 dead children with positive autopsies, 7 children with clinical syphilis, 13 children dead but with negative autopsies, 10 children discharged alive and well, and finally 23 children who died but did not come to autopsy. Upon deducting the latter, we have 110 syphilitic placentæ associated with 87 syphilitic children, a correspondence of 79.1 per cent.

From our calculation, it appears permissible to assume that the present investigation indicates that the microscopic examination of the placenta tallies with the clinical and anatomical findings in the child in from 80 to 90 per cent of the cases, which is in marked contrast to the 40 per cent obtained from a positive maternal Wassermann. Consequently, I am glad to find that this study confirms my previous impression, and indicates that the demonstration of the so-called Fränkel's disease in the placenta offers twice as great a probability of giving correct information concerning the condition of the child as a positive Wassermann on the part of the mother, and in the absence of a carefully conducted autopsy constitutes the most reliable means of diagnosis at our disposal.

In 1837 Abraham Colles announced that it was possible for a syphilitic father to engender a syphilitic child by a normal mother, and that the latter would remain immune to infection from her own child, while others might be infected by it. So much clinical evidence was gradually accumulated in support of the correctness of this statement that it became accepted as a dictum and is known as *Colles' law*.

Such an occurrence presupposes infection of the ovum by means of the spermatozoon, with the subsequent development

of immunity on the part of the mother. Presumptive evidence in its favor is afforded by the fact that comparatively few mothers of syphilitic children present a history of primary infection, and frequently give birth to a series of syphilitic children without ever developing signs of the disease. Fournier was an ardent believer in the doctrine, and his advocacy of the occurrence of so-called conceptional syphilis, or *choc en retour*, lent still further support to the probability of paternal infection. Indeed, it may be said that Colles' law was almost universally accepted up to 1903, when its applicability was denied by Matzenauer.

This is not the place, nor will time permit me, to trace the history of the controversy, except to say that with the discovery of the spirochete in 1903 and the description of the Wassermann reaction in 1907, more and more doubt has been cast upon the correctness of Colles' law, with the result that at present most writers, with the exception of Hochsinger, Boas, and Routh, absolutely deny its possibility upon both clinical and so-called scientific grounds.

This reaction was apparently placed upon a firm basis by the contribution of Bab, who pointed out that the relatively large size of the spirochete, as compared with that of the spermatozoon, made it *a priori* improbable that the former could be carried into the ovum by means of the latter. Consequently, he contended that the possibility of paternal infection must be denied, unless the existence of some sporadic or intermediate stage of the spirochete were demonstrated. As no such evidence has been adduced, he is inclined to deny the applicability of Colles' law. Furthermore, when the blood of pregnant and puerperal women, who were supposed to exemplify that law, was examined, it was almost uniformly found to present a positive Wassermann reaction. Consequently those interested in the subject concluded that the reason the mother did not become infected by her child was that she was already suffering from the disease, which for some unexplained reason existed in a latent form, and in many instances did not give rise to the usual manifestations.

It must be admitted that such reasoning is very plausible, and to a certain extent justifies the scepticism of those who cry "Away with Colles' law." Indeed, most arguments in its favor are far from convincing, and the recent one advanced by Routh, according to which infection of the ovum is effected by means of "gemmules" derived from the spirochete, is devoid of experimental basis; although, if its correctness could be demonstrated, it would solve many problems.

Notwithstanding the plausibility of the arguments against the correctness of Colles' law, my clinical experience has been such as to cause me to wonder occasionally whether such scepticism is entirely justified; and, while recognizing the difficulties in the way of adducing convincing evidence in its favor, to inquire whether it would not be more rational to regard the question as still *sub judice* rather than as actually disproved.

In the first place, the history of certain mothers of definitely syphilitic children seems to indicate that, if they are really the subjects of latent syphilis, the disease must be of a very

different type from that usually encountered. Upon going over the histories of the women presenting a positive Wassermann in our series, only a few could be found who gave any evidence of having had a primary sore, while in less than 20 per cent could a history of the usual secondary or tertiary manifestations be elicited. Furthermore, upon reviewing the patients, who had been in the service for many years, and many of whom had not been treated, we encountered very few who had exhibited the usual sequelae of the disease.

Merten had a similar experience, and reported that she had been able to elicit only a single history of definite infection in 48 women presenting a positive Wassermann during pregnancy. As the difficulty of detecting the primary lesion in women is generally recognized, it must be admitted that such negative evidence is of less value than in men, but, if a positive Wassermann during pregnancy be accepted as indubitable evidence of the existence of latent syphilis, I cannot rid myself of the impression that the disease must vary markedly from the usual type.

In this connection, one cannot avoid considering the possibility that a positive maternal Wassermann during pregnancy may occasionally be regarded as a manifestation of the establishment of active immunity on the part of the mother against a syphilitic product of conception. Of course this implies the acceptance of spermatic infection, but if such a possibility were once admitted, for which at present there is no scientific basis, it would be easy to comprehend the mechanism by which such immunity might be established from what we know concerning the invasion of the maternal by fetal tissues and concerning the deportation of chorionic villi during pregnancy.

Suggestive evidence along such lines was afforded by three cases in the present series. In each of them the patients, who presented a positive Wassermann and were not treated during pregnancy, gave birth to syphilitic children, but upon repeating the Wassermann some weeks or months later we were surprised to find that it had become negative. That this is not an isolated experience is shown by the fact that Merten, upon repeating the Wassermann within two weeks after labor upon 26 women, who had exhibited a positive reaction during pregnancy, but who had not been treated, found that it had become negative in 14 and had remained positive in 12 cases. By means of various controls she convinced herself that the conversion could not be regarded as due to errors in technique, and consequently she concluded that it resulted from some deep-seated change in the economy of the women. Furthermore, Dr. Albert Keidel of the syphilitic division of The Johns Hopkins Hospital informs me that such changes are not unusual in his experience. No satisfactory explanation has yet been offered in explanation of this phenomenon, so that all that can be said is that it might be regarded as presumptive evidence in favor of Colles' law, if the possibility of spermatic infection were established.

Turning to another side of the question, it may be asked, if the presence of a positive maternal Wassermann during pregnancy is to be admitted as evidence of the existence of latent syphilis, what can be said of the 65 women included in Chart

II, who presented a negative Wassermann during pregnancy, but yet give birth to 43 definitely syphilitic children? I must confess my inability to answer the question, and, while numerous suppositions might be advanced, I shall content myself with pointing out that as yet we know too little concerning the significance of the Wassermann reaction to feel justified in making dogmatic or *ex cathedra* statements.

In addition to these somewhat dubious reflections, I have seen several patients in whom the theoretical possibility of Colles' law was very great. One of them, who had double ovum twins, appears to afford presumptive evidence in favor of Colles' law associated with superfecundation. The history is as follows: In 1896 and 1897 this colored patient had her fifth and sixth spontaneous labors in our out-patient department. On September 26, 1898 (Out-patient service No. 502), when 27 years of age, she gave birth spontaneously to premature male double ovum twins. The first weighed 4 and the second 4½ pounds; the former was raised, while the latter, which was asphyxiated when born, died in three hours. Autopsy (No. 1153) was done, and the following anatomical diagnosis was made: "Congenital syphilis, syphilitic cirrhosis and interstitial splenitis; interstitial pneumonia; thickening of epiphyseal lines; ecchymoses of epicardium; patent foramen ovale." Microscopic examination of the two placentæ showed that the first was normal, while the second presented typical syphilitic lesions. In other words, one of the double ovum twins was syphilitic, and the other normal.

Upon attempting to find an explanation for this unusual occurrence, the patient was closely questioned, and admitted that she had intercourse both with her husband and with a lover, who was found to be under treatment for syphilis in the genito-urinary service. As all of the six children born prior to the twins had been normal, and as the microscopic examination of the placenta from the sixth was negative, we allowed ourselves to make the somewhat phantastic diagnosis of superfecundation, and assumed that the ovum for the normal twin had been fertilized by the husband and that for the syphilitic one by the lover.

The subsequent history confirmed this supposition, for following the twins the patient had 11 other full-term spontaneous labors with live children, the last one being born on May 8, 1912 (Out-patient service No. 5527), when the patient was 41 years old. Microscopic examination showed that all of the placentæ were normal.

As the twins were born years before the discovery of the spirochete and the Wassermann reaction, no information along such lines was available at that time. In 1916, however, we looked up the patient, and found that she was in good condition and at no time had presented symptoms referable to syphilis. Both she and her husband presented a negative Wassermann, but unfortunately the test could not be made upon the remaining twin as it had died during childhood.

I do not care to be understood as claiming that this case offers irrefutable evidence in favor of Colles' law, but a little

reflexion must convince the most sceptical that it is highly suggestive. In this instance, we have records of the microscopic examination of the placentæ from the labor preceding and from the 11 labors following the supposed superfecundation, and all were normal. Furthermore, all of the other children were born in good condition, and were somewhat above the average in weight. Consequently, it may be safely affirmed that the only evidence of syphilis in the remarkable reproductive career of this patient was in one of the double ovum twins. Furthermore, it may be inferred; had the husband been responsible for it, that some of the other children would likewise have presented evidences of the disease, but as this was not the case, it seems permissible to surmise that the lover was responsible for it, in which event it could only be explained as due to paternal infection and that the mother exemplified Colles' law.

In several other instances histories were encountered which can most readily be explained as resulting from spermatic infection and as exemplifying Colles' law.

I shall refer briefly to one such patient (History O. 7279; O. 7766 and O. 8362). In this instance the patient, who previously had five spontaneous labors with normal children, gave birth to a premature macerated syphilitic child in 1916. As her Wassermann was negative, that of the husband was taken and found to be positive. Neither was treated. In 1917 she gave birth to premature macerated syphilitic twins. Again her Wassermann was negative and the husband's positive. Again neither was treated. The following year she returned early in her eighth pregnancy with a negative Wassermann. That of the husband was still positive. The patient was then treated intensively with the result that she had a normal child at full term, with a normal placenta. The husband was not treated. The child was discharged in excellent condition, 112 grams above its birth weight. Unfortunately, however, neither it nor its parents could be located in March, 1920, when we attempted to learn its ultimate fate.

Of course it must be admitted that such a history does not afford conclusive evidence in favor of paternal infection nor of Colles' law, but at the same time it creates a strong presumption in their favor, which to my mind is more convincing than the evidence which is usually relied upon to prove their impossibility.

I shall not attempt to carry the argument further and shall conclude by stating that in my opinion the possibility of spermatic infection and the admissibility of Colles' law have not yet been conclusively proven or disproven, and consequently should be regarded as still *sub judice*.

It is scarcely necessary to add that the collection of the data upon which this paper is based has entailed an enormous amount of routine work on the part of members of the obstetrical staff, as well as of several members of the pathological staff. Consequently, I take this opportunity to express my appreciation of painstaking efforts of a considerable number of collaborators without whose aid the work could not have been completed.

## THE CELLS OF THE ARACHNOID

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During the past few years there has been evident in the literature a renewed interest in the physiological anatomy of the leptomeninges. The published studies have been primarily devoted to the arachnoid and the pia mater as constituting a membranous pathway for the cerebrospinal fluid; in the earlier years attention was paid merely to the morphology of the cells lining this fluid-containing subarachnoid space. More recently, however, the combined work of several investigators has afforded a more definite and concise conception of the morphology of these lining cells, so that it now becomes possible to present data regarding the changes in form of these cells under certain physiological conditions and to describe other changes resulting apparently from the age-condition of the animal at the time of study. It becomes the purpose of this paper, therefore, to present this conception of the varying morphology of the cells lining the subarachnoid space and to point out as far as possible the conditions which determine these changes in form of the cells.

### GENERAL MORPHOLOGY OF THE CELLS LINING THE SUBARACHNOID SPACE

For a better understanding of the relation of the cells lining the subarachnoid space to the cerebrospinal fluid, a brief anatomical description of the leptomeninges is necessary. Such descriptions have recently been given in other places (Weed<sup>1,2</sup>; Essick<sup>3</sup>); here only the essential characters will be outlined. The outer of the two more delicate investing membranes of the central nervous system—the arachnoidea—is customarily described as a thin continuous membrane, of a glistening external surface beneath the dura, bridging the cerebral sulci and containing beneath it the cerebrospinal fluid. But such a picture of the arachnoid is not complete as it takes account only of the more obvious continuous character of this leptomeninge. In reality this structure should be arbitrarily divided into two parts, the arachnoid membrane (the outer continuous cell-layer investing the whole central nervous system) and the arachnoid trabeculae (the cell-columns which stretch from the inner surface of the arachnoid to the pia mater).

The arachnoidea becomes, then, a cellular structure with a delicate supporting reticulum, covered on both sides by characteristic cells. From the inner side of this membrane project small delicate trabeculae, upon which are continued the cells forming the inner lining of the arachnoid membrane. The larger of the trabeculae possess a core of a few connective-tissue fibrils, united on the outer side with the fibrous framework of the arachnoid membrane and on the inner side with the subpial tissues; the smallest trabeculae seem to be composed merely of the cytoplasmic processes of the lining cells. The lining cells, reflected from the inner surface of the arachnoid membrane and continued upon the trabeculae, become the

cells covering the pia mater, for this innermost membrane of the central nervous system is formed by this reflection of the lining cells, supported by a few connective-tissue fibrils and neuroglial elements.

Between these two membranes, the arachnoidea and the pia mater, is the subarachnoid space; it is really merely an intra-leptomeningeal fluid-channel. The passages through this space are interrupted by the arachnoid trabeculae so that the circulating cerebrospinal fluid must traverse a devious, tortuous, but continuous channel. Essick<sup>3</sup> (p. 380) has likened the pia mater and arachnoid to "a living sponge accurately filling the irregularities between the brain and the dura. . . . Just as the spaces in a sponge are in free communication, so the cerebrospinal fluid is normally continuous everywhere."

The occurrence of this web-like network in the subarachnoid space represents a partial persistence of certain characteristics of the embryonic structure of the leptomeninges. Studies on the development of the cerebrospinal spaces have indicated that the meningeal channels arise by a dilatation of the meshes in the perimedullary mesenchyme, resulting in rupture of many of the cytoplasmic strands and in the formation of the permanent arachnoid trabeculae (Weed<sup>1</sup>). The cells of this mesodermal tissue become modified in their development to form the typical lining cells of the subarachnoid space. Likewise, similar mesodermal elements differentiate to form the cells lining the inner surface of the dura and the outer surface of the arachnoid membrane. With such a developmental history it seems quite proper to term them "mesothelial" cells.

Morphologically, these covering cells of the leptomeninges are of a low flat form, with large, pale, oval nuclei. The chromatin net in the nucleus is usually only indistinctly made out. With ordinary histological stains the cell boundaries are not visible, but definite intercellular lines may be demonstrated by silver nitrate (Key and Retzius,<sup>7</sup> Essick<sup>3</sup>). The cytoplasm of these flattened mesothelial cells contains fine granules which are of larger size near the nucleus as shown in the excellent plates of Key and Retzius. These authors also described in the arachnoid cells fat-like material, which, though staining with osmic acid, did not give the dense black of the ordinary fat-droplet.

Study of the morphology of the cells of the arachnoid in ordinary histological sections is by no means as satisfactory as when made upon spread-preparations. In these, the arachnoid membrane is dissected away under binocular microscope by sectioning the arachnoid trabeculae as near to their pial attachment as possible. The delicate membrane is then mounted on a slide with the outer surface down, so that the isolated and freed arachnoid trabeculae are presented for study. This permits direct observation of the cells of the inner surface of the arachnoid and particularly of those covering the arach-

noid trabeculae. The dissection of the arachnoid in the spinal region is not difficult but over the cerebral hemispheres the procedure is complicated by the delicacy and fineness of the arachnoid mesh. With this method excellent pictures of the typical flat mesothelial cells can be obtained.

These mesothelial cells are usually so placed on the surface of the leptomeninges that they are of only one cell in thickness. At times the number of cells in a given area of membrane is increased and the cells are of more than one layer in thickness; these areas of reduplication of the cell-covering become evident in both histological sections and in spread-preparations. Under normal conditions the cells of the leptomeninges are of the low, flattened type indicated, with a granular cytoplasm and pale oval nuclei. Everywhere throughout the cranial and spinal regions this typical morphology holds.

#### CHANGES IN THE CELLS UNDER PHYSIOLOGICAL ACTIVITY

It was noted in 1917 that the general morphology of the cells of the leptomeninges "depends apparently not only on their situation but also on their physiological state." (Weed,<sup>14</sup> p. 467.) The evidence for the latter part of this statement was based upon the changes in the arachnoid cells in response to the injection of particulate matter into the subarachnoid space. Within a few hours after such injections of carbon granules (India ink) the cells of the arachnoid were found to contain the particles; with cinnabar a similar cellular reaction was observed, phagocytosis of the granules in this case being not as widespread nor as active as with the wholly inert carbon granules. Under such experimental conditions, with the cerebrospinal fluid filled with the foreign particulate matter, the cells became larger, rounded up and assumed somewhat cuboidal forms. Largely because of the frequency with which these appearances of cuboidal form were met with in the specimens injected with particulate matter, the general descriptive appellation of "low cuboidal cells" was applied to the cells of the leptomeninges. Although, when used, this term was qualified by reference to the customary flat morphology, it does not, in view of the more extensive knowledge of the physiological reactions of the cells now possessed, seem longer justified. Additional argument for the use of another adjective in the descriptions of the cells of the arachnoidea has been based on the changing morphology of these cells as they invade the dura mater in certain restricted areas and become the typical cell-columns of the pachymeninx (Schmidt,<sup>15</sup> Weed<sup>16</sup>). Such cell-columns are normal structures; their occurrence makes the qualification that the morphology of the cells of the arachnoid depends not only on their location but also on their physiological state justifiable. Yet in the description of the cells lining the subarachnoid space, emphasis on the normal flat character of the resting or inactive cell should continue to be placed.

Following these primary observations that the cells of the arachnoid changed their morphology in response to particulate matter in the subarachnoid space, Essick<sup>17</sup> greatly extended our knowledge of the physiological response of these cells to other kinds of particulate matter. His observations were made

almost entirely on spread-preparations of the spinal arachnoid; the isolated trabeculae afforded an excellent opportunity for the study of the reactions of the isolated cells. Staining of the isolated portion of the arachnoid membrane with dilute solutions of toluidin blue permitted satisfactory histological studies.

The most striking reactions of the arachnoid cells Essick found to follow the subarachnoid injection of laked blood. The blood was prepared by laking with distilled water and restoring the solution to isotonicity by adding suitable quantities of a stronger solution containing sodium chloride, potassium chloride and calcium chloride. Such subarachnoid injections of partially hemolyzed red corpuscles caused a marked sterile meningitis within six hours; this inflammatory process subsided rapidly, becoming almost quiescent at the end of 48 hours. During the latter part of this reaction, the cell-content of the cerebrospinal fluid changed from a polymorphonuclear to a large mononuclear element. These large mononuclear cells possessed all of the characteristics of the amoeboid macrophage, to use Metchnikoff's designation as qualified by Evans.<sup>18</sup>

Under these experimental conditions Essick found great changes in the morphology of the cells of the arachnoid, when studied in spread-preparations. The protoplasm of the cells first increased in thickness so that the nuclei no longer stood out sharply on profile view, and this increase in volume of protoplasm about the nucleus continued, while the nuclei became more circular in outline. Gradually the attachment of these cells to the framework of the trabeculae or membrane became less broad and inclusions of fragmented red cells appeared within the cytoplasm. Many of these phagocytic cells then became detached, to form the free round phagocytes, identified in the cerebrospinal fluid. Similar changes in the morphology of the covering cells were made out in the outer surface of the arachnoid membrane, following the accumulation of blood in the subdural space. When the phenomenon of budding-off of these cells was outspoken, many mitotic figures were seen in the membrane.

Essick further studied the reaction of the cells of the arachnoid to dilute suspensions of carbon and cinnabar granules. While the formation of free macrophages was not as frequent as with the laked red cells, the same process of phagocytosis of granules and swelling of the protoplasm was observed. Although the reaction of the cells of the arachnoidea to these granules was not as vigorous as with the blood, the same biological change in morphology to both varieties of particulate matter seemed established. Schott<sup>19</sup> and later Goldman<sup>20</sup> had shown that both the pleural and the peritoneal surfaces could furnish free-moving phagocytic cells; the same physiological reaction, as with the mesothelial cells of true serous cavities, occurred in the mesothelial cells of the subarachnoid space.

In studies of the reactions in the subarachnoid space to infective processes, Ayer,<sup>21</sup> working contemporaneously with Essick, observed at times an essentially similar change in the morphology of the lining mesothelium. In many early acute cases of experimental meningitis the cellular exudation in the meninges was of the large mononuclear type; Ayer stated,

from a study of transitional stages in the cells still attached to the membrane, that at least some of these cells represented macrophages derived from the arachnoidea. In the presence of the toxins of such early infections, the mesothelial cells became larger, with accumulation of the cytoplasm about the nuclei; the cell-attachments became less extensive and in sections the cells appeared as if ready to be detached. The many complicating factors in such infections, however, rendered more exact statement of the reactions of the cells of the arachnoid impossible.

The evidence, then, supports the view previously expressed (1917) that the morphology of the mesothelial cells of the arachnoid depends at least in part upon the physiological state of the cells. While normally the cells are of a flattened, very low type everywhere over the arachnoid membrane, they become, in response to the stimulus of particulate matter (carbon, cinnabar, fragmented red cells, etc.), as well as in certain acute infective processes, enlarged and elevated, with inclusions of foreign material within them.

#### CHANGES IN ARACHNOID CELLS CONDITIONED BY AGE

In 1859, Meyer<sup>6</sup> described abnormal aggregations of cells in the arachnoid as "Die Epithelsgranulationen der Arachnoidea," a post-mortem finding in the brains of patients suffering from mental disease. These observations of Meyer's have not been extensively quoted in the literature and the phenomenon has not been satisfactorily described. In a paper by Cushing and Weed<sup>7</sup> "a peculiar proliferation of the arachnoid mesothelium of a cat" was recorded. This cellular overgrowth was observed in but a small proportion of laboratory specimens (man and ordinary laboratory mammals); no ages were given for the animals in which the process was noted, though the first animal was recorded as a "young adult" cat. It was thought at the time that the proliferative "process was almost invariably associated with the deposition of lime salts in the membrane." Subsequently, Essick<sup>8</sup> described similar areas of thickening in the arachnoid membrane: "Distributed throughout the brain and cord are clusters of closely placed nuclei within the arachnoid membrane. . . . Such areas are irregular in shape, size and distribution. . . . They represent normal structures and, like the arachnoid trabeculae, become the seat of calcium deposits with the advancing age of the animal. In no sense should they be mistaken for a cellular proliferation in response to a degenerative process."

It has been my intention for several years to study these cell-masses in the arachnoid membrane more thoroughly and to present as far as possible a more complete description. As isolated fragments of evidence accumulated in the study of the leptomeninges both in normal and in infected animals, it became more apparent that the age of the particular animal was one of the most important, if not the determining factor in their occurrence. The cell-nests had been met with in practically all of the laboratory animals as well as in man; their occurrence in all of these species indicated that their biological significance was great.

Recently a series of cats was chosen with particular reference to the age of each animal as determined by general appearance, condition of teeth, etc. While this determination of age of the cats could never be made with thorough exactness, the animals could roughly be classed according to their age without much error. Each cat, as soon as the determination of approximate age was made, was weighed and then killed with ether. The thorax was opened immediately thereafter and a cannula inserted through the left ventricle into the aorta. Customarily the blood was washed out by perfusion with warm Ringer's solution; on the venous side an outlet was provided by making a small incision into the tip of the right atrium. As soon as the perfusing fluid became clear, an injection of 10 per cent formalin was made through the aortic cannula and the atrial opening clamped. About one liter of fluid was usually injected under a pressure of 900 millimeters of fluid. Subsequently, the calvarium and arches of the vertebrae were removed and the central nervous system was further fixed by immersion in formalin. Finally, the bony structures were entirely removed, and the central nervous system, still surrounded by intact meninges, was left in the formalin until studied. When examined, the dura over the cerebral hemispheres was carefully opened and the underlying arachnoid lightly stained with a dilute solution of toluidin blue or of methylene blue. The dura of the spinal cord was likewise carefully opened and the same stain applied to the exposed arachnoid membrane.

When examined under the binocular microscope, the meninges of this series of cats could be easily divided into two groups: those which showed cell-accumulations in the arachnoid membrane and those which presented a smooth, regularly staining surface. In the former group, the arachnoid membrane, particularly over the hemispheres where the study could be made with great ease, showed irregular, discrete, more densely stained areas. Even in the gross, these areas of deeper stain could be made out, and the exposed membrane over the cortex presented a mottled appearance. There was usually great variation in the shape and size of these more densely stained areas: at times they were circular with sharply defined borders; again they were irregular and faded gradually off into the adjacent thin arachnoid membrane and occasionally they represented mere fusiform thickenings of the membrane. In some animals, only a few, small, ill-defined masses appeared over the whole arachnoidea; in others the membrane was thickly covered with the more densely stained nodules. Frequently in the more definitive areas of cell-accumulation oval or rounded glistening bodies were identified in the midst of the deeply stained masses; structurally these glistening bodies seemed unlike the remainder of the membrane.

The distribution of these more densely stained areas in the arachnoid membrane was fairly well demonstrated by such macroscopic examinations. In those animals in which the masses were few in number and quite minute, the greater number of nodules, in the cerebral portion of the nervous system, appeared in the arachnoid as it bridged the larger sulci, particularly in the cruciate and sylvian regions. In the spinal cord, the distribution seemed more regular and without great

differences in localization; in general the ventral surface of the cord seemed practically uninvolved in the process, while the dorsal half showed many of the deeply stained areas. Quite similarly in the brain, the ventral surface of the brain stem was practically always free from the nodules, even though the cerebral cortex might be extensively covered; in only one case of the series was a typical more densely stained area made out on the basilar surface.

These more densely stained areas, so clearly shown in this relatively gross examination, were easily resolved, under higher powers of the binocular microscope, into deeply stained nuclei, rather closely packed together. Elsewhere than in these areas of differentiation, the arachnoid membrane presented more or less regularly placed nuclei, not closely approximated to one another but separated by appreciable distances. In the densely stained area, the nuclei were closely gathered together and separated by but little lightly stained cytoplasm. Occasionally in the midst of such a nuclear aggregation, there could be made out a diffusely stained, more or less homogeneous substance without definite structure. And again, oval or spherical masses taking a fairly dense stain stood out in contrast to the adjacent closely approximated nuclei.

When blocks for histological sections were cut so that the leptomeninges remained attached to the underlying brain substance, the characteristics of these more densely staining masses were brought out even more vividly than by examination under the binocular microscope. Sections both perpendicular and tangential to the nervous tissue were employed for this purpose; in general, the perpendicular sections afforded the better opportunities for study. In such preparations, the more densely stained areas seen in the gross examination were easily identified as localized thickenings of the arachnoid membrane, characterized by considerable aggregations of closely packed nuclei and varying amounts of protoplasm (Figs. 1, 2, 3 and 4). These nodular masses varied markedly in size and in form, being at times sharply delimited from the adjacent membrane or diffusely merging with it. The nuclei were in general somewhat more rounded than the typical oval nuclei of the arachnoid cells elsewhere; the chromatin-content in some of the nuclei was diminished, while in many other cells there seemed a slightly increased amount. The cytoplasm of the cells comprising the nodular swelling contained some granular inclusions near the nuclei, but not in as definite form nor so regularly distributed as in the ordinary arachnoid cell (*cf.* Key and Retzius<sup>7</sup>). In the cell-mass, intercellular borders were not distinguishable by the ordinary histological stains. In general the nuclei were very closely packed together (Fig. 1) but in other areas the relative amount of cytoplasm was greater (Fig. 4). Even in the nodular swellings themselves the tendency to irregular massing of the nuclei was great (Figs. 2 and 3) and formations of small whorls were evident.

Many of these arachnoid cell-clusters appeared in section to be very sharply circumscribed aggregations of cells; the transition was not wholly abrupt but there occurred a small prismatic area of enlargement at each pole of the oval swelling.

The occurrence of such a cell-mass did not seem to affect the cells in the immediate neighborhood; these showed no histological evidence of change from their customary flattened form. In other situations, even at times in the same animal, the typical arachnoid cell-cluster formed merely the most prominent part of a diffuse thickening of the whole membrane as illustrated in Fig. 2 and to a lesser extent in Fig. 3. Certainly in these cases, the tendency toward change was met by the body in a slightly different way, so that the cell-alteration in the one case was confined to a very definite locus and in the other to a more diffuse and extensive area. No difference in significance of the two types of swellings has been made out.

Certain phases of the relations of these arachnoid cell-clusters were of particular interest. In the case of the localized, definitive enlargement the general impression derived from examination of the sections was that the whole cell-cluster could be easily shelled out from the membrane (Fig. 1). With the more diffuse swelling (Fig. 3) this impression was not given, the diffuse cell-cluster remaining an integral part of the membrane in every way. With both types of swelling, however, the inner surface blended intimately with the delicate and irregular arachnoid trabeculae (Figs. 1, 2, 3 and 4). But most interesting of the relations of these nodular masses were those of the outer surface of the membrane. It has been known for some time (*cf.* Schmidt,<sup>10</sup> and Weed<sup>11, 12</sup>) that there exist, scattered irregularly throughout the subdural space, prolongations of the arachnoid membrane into the dura; these cellular extensions are connected for the greater part with arachnoid granulations in the dura. In other places, the arachnoid seems to be incompletely separated from the dura so that small but definite areas of fusion exist—a phenomenon which might well be predicted by consideration of the embryology of the two membranes (Weed<sup>13, 14</sup>). The frequency of attachment of the arachnoidea to the dura becomes apparently much greater in the sites of development of the typical cell-clusters. In many instances in the present series of animals it was almost impossible to separate the two membranes in such localities without damage or lifting away of the cell-cluster; Fig. 4 shows well the result of such an artificial separation. Here the outer surface of the arachnoid membrane is shown above; the cell-nodule has been lifted away from its bed in the arachnoid membrane and the loose outermost strands of the surface have been torn away. The connection of such cell-clusters to the dura did not seem to be very firm but the adhesion was definite and important.

If the arachnoid cell-cluster be looked upon as an area of active hyperplasia of the membrane, one should expect to find many mitotic figures in the cells of the mass. Extended search for such evidences of cell-division has been made, but only very rarely could such a figure be identified. It must be assumed therefore that the initial processes resulting in the formation of such cell-clusters were probably slow and continued over a relatively long period of time; the cell-growth is in no sense to be considered a rapid, wholly unrestrained proliferation of the covering cells of the membrane.

When the occurrence of these arachnoid cell-clusters was related to the records of the approximate ages of the cats in the series, it became at once apparent that the very old animals in every case showed such cell-aggregations in the arachnoidea. In the very young animals, the cell-clusters were never found; in adults, in which senile changes were not obvious in the general examination, the cell-clusters were occasionally encountered. It seemed obvious, therefore, that the presence of the cell-clusters was conditioned upon the age of the particular animal; their absence in the immature and invariable appearance in the old indicated that during adult life there occurred changes which finally resulted in the development of the cell-clusters. In the adult animal, the tendency to the cell-hyperplasia in the arachnoid increased as the animal grew older. Variations in the number of the cell-clusters were found in animals equally senile; no significance could be attached to this finding. The relation of the age of the animal to the occurrence of such cell-clusters seemed established.

#### ULTIMATE CHANGES IN THE ARACHNOID CELL-CLUSTERS

It becomes, of course, a matter of interest to determine the fate of these relatively frequent cell-clusters in the arachnoid membrane. Meyer<sup>6</sup> described, in the epithelial-granulations he recorded, the occasional infiltration with calcium salts. Cushing and Weed<sup>7</sup> noted that the cell-clusters were a common site of the process of calcification in the arachnoid. They stated (p. 368) that "though the proportion of laboratory specimens in which we observed examples of cellular hyperplasia was small, the process was almost invariably associated with the deposition of lime salts in the membrane." Essick<sup>8</sup> presented a similar view when he wrote (p. 381) that the arachnoid cell-clusters "represent normal structures and, like the arachnoid trabeculae, become the seat of calcium deposits with the advancing age of the animal." Study of the present series of specimens has led to the view that calcification represents but one phase of the ultimate fate of these cell-nodules; a second somewhat more striking reaction is represented, not on the side of degeneration (as in calcification) but in an outspoken proliferation which apparently results in neoplasms.

Cushing and Weed<sup>9</sup> gave a detailed account of the formation of calcareous nodules, tracing the histological history of the psammoma bodies or corpora amylacea. The early evidences of the process of calcification were shown to occur at times in the nuclei of the arachnoid cells; at other times, in the cytoplasm of the cells. Notation was made of the formation of whorls in the areas of hyperplasia of the arachnoid mesothelium; this arrangement of the cell nuclei was especially frequent about the calcareous nodules.

With this view, expressed five years ago, the deductions from the present study largely coincide. But the initial formation of the arachnoidal cell-cluster in the membrane may be best considered as a phenomenon of advancing age in the individual; such cellular nodules represent an almost invariable process of hyperplasia in senescence. Apparently the cell-nests reach only a limited size; they never become, as judged

from the many specimens studied, very large, usually attaining a maximum diameter of one to three millimeters. Many seem to persist without showing any signs of degeneration, remaining of a constant size or possibly slowly increasing in one or other diameter. Others in the same animal undergo degeneration with the infiltration of calcareous material. In no specimen studied, however, did more than three-fourths of the cell-clusters show signs of this calcareous degeneration; it is highly probable, however, that any extreme case might exhibit calcification in practically all of the nodules.

The degeneration of the cells of these nodules in the arachnoid may be connected with the relatively poor vascular supply to the arachnoid membrane. According to the best anatomical observations the arachnoidea is practically devoid of capillaries and in these cell-clusters there seems to be no evidence of new formation of a vascular bed. The earliest form of degeneration consists apparently in a change of the substance of the cells into an amorphous hyaline-like material in which only vague shadows of cell-bodies exist (Fig. 5). Whether this is a stage in the formation of a real calcified body cannot be told; certainly, as shown by Cushing and Weed, the calcareous deposition may occur in nucleus and in cytoplasm in very minute but histologically detectable masses. But these areas of amorphous degeneration many times occur in the same arachnoid cell-cluster as a definite calcareous body (Fig. 6); the two processes may then proceed simultaneously, the one possibly representing the initial stage of the other.

When the process of calcification in the cell-clusters becomes outspoken, the calcified body may assume the shape of a rather imperfect sphere in which on section concentric rings are evident (Fig. 7). In other nodules the calcium deposit is very irregularly placed (Figs. 6 and 7), the deposition being incomplete or involving only a portion of the area of degeneration. At other times the area of calcification in such an arachnoid cell-cluster may be quite limited and the remainder of the cell-cluster relatively unaffected. Such a condition is illustrated in Fig. 8, in which a large calcareous body appears to the left, while elsewhere in the cell-cluster the nuclei show but little evidence of change, though the more darkly shaded areas seem to be the seat of an early change. Surrounding the definite calcareous masses, the arachnoidal cells frequently show typical whorl-formation as in Fig. 7. In other cases, however, the area of calcification may involve the whole cellular area, the cells not being grouped into whorls. While this tendency toward whorl-formation is so frequently met with about the calcified bodies, it must not be interpreted solely as a reaction to the calcified body but rather as an expression of a peculiarity of the cell-growth in the arachnoidea as well as elsewhere. For the occurrence of similar whorls in the cell-clusters of the arachnoid (Figs. 1 and 3) has already been emphasized.

That calcareous degeneration is not the sole pathological change to which these arachnoidal cell-clusters are subjected was demonstrated by the findings in two animals in this series of cats. In both of these, masses involving the cerebral arachnoid were found on opening the dura; in the first animal the initial impression was that the arachnoidal cell-clusters were

exceptionally large and exceptionally well differentiated from the membranous expansion of the arachnoid, while in the second obvious masses of new-growth were apparent. In this second animal two relatively large tumors of rather tough, glistening tissue were found, the one in the left sylvian fissure while the other was closely attached to the falx cerebri on the same side, displacing the substance of the cerebral cortex and blending intimately with the leptomeninges. In the first of the two cases, the diagnosis from gross examination was impossible; in the second cat, a tentative diagnosis of cerebral neoplasm seemed justified.

Microscopically, the leptomeninges in the first of these two animals showed a rather small, definitely circumscribed new-growth with all the characteristics of the so-called dural endothelioma in man. The mass showed an increased number of rather deeply stained, oval nuclei with relatively sparse cytoplasm; the cells were for the greater part arranged in whorls and surrounded in many places typical calcareous bodies (Fig. 9). The tumor seemed quite well vascularized, and in the fixed tissue spaces between the whorls are numerous. The mass was situated in the outer portion of the arachnoid membrane, leaving a well-marked subarachnoid space between it and the brain-substance. The dura covering the mass showed a slightly roughened area of attachment without evidence of invasion of the dura by an arachnoid cell-column; the line of cleavage, however, on lifting the dura was between the dura and the tumor. This phenomenon of partial attachment of the abnormal cells of the arachnoid to the dura was essentially similar to the attachment of a typical cell-cluster to this membrane. Histological examination of other blocks taken from the brain of this animal showed many arachnoidal cell-clusters, some of which contained calcareous bodies, but no other tumor mass.

Similar, but much larger, endotheliomata were found in the second of the two cats. Here in both of the areas in which macroscopically abnormal growths were made out, tumors of the same type, rather widely separated and in no way connected with each other, displaced the brain substance. The tumors seemed on microscopic examination to be somewhat more actively growing than in the case of the small tumor in the first cat (Figs. 10, 11 and 12). The tumor cells were for the most part arranged in whorls of greater or less size; occasionally (Fig. 12) a large whorl contained within it a series of these smaller concentrically arranged cell-nests. Histologically, the individual tumor cells were of typical form with oval, rather deeply stained nuclei and with varying amounts of cytoplasm. The vascular channels, comprised of rather large vessels with thin walls, were quite abundant in these two larger growths. Small round or irregular calcareous masses were very common (Figs. 10 and 11); about these bodies the cells were arranged in the characteristic whorl. In other places the calcium was laid down in a more or less extensive plaque; in Fig. 12 a large crescentic mass covering a half of the periphery of the spherical tumor is shown. An extensive connective-tissue framework of the tumor was revealed by Mallory's stain which outlined the cell-whorls with circular fibers. In

every way, the histological picture was that of the typical "dural endothelioma" of man.

The relation of these tumors to the dura mater are of interest. In the first of the tumors (Fig. 9), the separation on raising the dura came between dura and arachnoid; there existed, however, a rather intimate but easily broken attachment of the tumor to the dura. This adhesion was easily made out in microscopic sections; some evidence of the torn filaments appears in the photomicrograph. In every way, the dural relations of this new growth were quite similar to those shown in Fig. 4, where the separation of the dura and arachnoid resulted in the lifting up of the arachnoid cell-nest from its bed in the membrane. The connections of the endotheliomata to the dura in the second cat were quite different from those in the first. Here (Figs. 10 and 11) the new-growth was very closely attached to the dura, so that the tumor appeared to have arisen from this dense fibrous membrane. The connective tissue of the endothelioma blended, as shown by Mallory's stain, with the dural connective tissue.

This intimate attachment of the tumor to the dura is quite similar to the usual arrangement in man; it has resulted in the designation of these tumors as "dural endotheliomata." Consideration of the findings in the case of the arachnoidal cell-nests and of the endothelioma in the first of the two cats leads to the suggestion that, in at least some of these instances, the dura attachment is secondary to the initial growth of the tumor, dependent upon other factors, such as the possible subsequent development of vascular channels from the dura mater.

Of course it is very difficult to decide with exactness the point of origin of any differentiated tumor mass. In the growth of the endotheliomata of the meninges, the evidence at hand suggests strongly that they arise as a proliferative phenomenon from the initially slowly growing arachnoid cell-cluster. The somewhat similar type of cell, the occurrence in both growths of typical cell-whorls, their common calcareous degenerations, and their apparent identical topographical relations in the arachnoid membrane seem greatly in support of this conception. In a somewhat different sense, Schmidt<sup>20</sup> considered the endotheliomata to be arachnoidal in origin and an essentially similar viewpoint was expressed by Cushing and Weed<sup>21</sup> as follows (p. 371): "The so-called dural endotheliomas show histologically the same cellular arrangements with calcareous and osseous depositions that are commonly found in the arachnoid and therefore take their origin in all probability from the mesothelium of this membrane." To these hypotheses of arachnoidal origin of the endothelioma, the present findings in the cat add support; the greater evidence to-day seems to depend upon the very common occurrence of the arachnoid cell-clusters in adult and old animals. Between the true tumor and the cell-cluster, are transitional types—large elongated cell-clusters in the arachnoid in which the cells resemble more the tumor cell, of apparently more active growth. Such specimens were found in two of this series of cats; while classed with the arachnoid

cell-clusters, their appearance suggested strongly the endothelioma.

The arachnoidal origin of such endotheliomata may at times be really intra-dural, from the columns of arachnoid cells normally present in the pachymeninx. These intra-dural collections of the arachnoidal mesothelial cells are connected with the prolongations of the arachnoid membrane into the dura; the cells are rather closely packed together and surrounded by the dense fibrous tissue of the dura. Histologically these cell-columns are essentially similar to the arachnoid cells in a typical cell-cluster. Schmidt's<sup>10</sup> studies led to the conclusion that the endotheliomata were arachnoidal in origin, and were particularly related to the intradural arachnoid cells covering the Pacchionian granulations or those invading the dura as arachnoid cell-columns. Wojna<sup>11</sup> has pointed out the relation of similar aggregations of cells to physiological herniation of the brain; these observations are of interest in showing the importance of such intradural aggregations of cells. If the endothelioma should arise from such a cell-nest within the dura, its connection to the dura would be intimate and primary; if from the cell-cluster in the membrane it would be possibly equally intimate but in every respect secondary.

#### DISCUSSION AND SUMMARY

From the data gathered together in the foregoing pages it becomes possible to present a more definite conception of the cells of the arachnoidea. While normally in the resting state, the cells covering the arachnoid membrane on its outer surface and lining the subarachnoid space are of a low flattened form, this morphological character changes with alteration of the physiological state and in the altered conditions of advancing age. Thus in response to the stimulus of particulate matter, the arachnoidal cells enlarge, become phagocytic, and multiply, some becoming under appropriate conditions free-moving macrophages in the subarachnoid space. An essentially similar response of the cells occurs in the early stages of certain acute infections of the meninges. That the cells of the arachnoid react in a similar way to such widely varying stimuli would indicate that the phenomenon is the morphological expression of an essentially similar alteration in the functional state of the cells.

A second change of significance in the cells of the arachnoid membrane is that of the slow hyperplasia of the mesothelial elements to form well localized cell-clusters in the membrane. These cell-masses occur in adult animals, particularly in those in which signs of advanced age are apparent. The phenomenon of this cell-overgrowth has not been observed in young animals in any instance; the hyperplasia is determined apparently by the age-condition of the particular animal. These cell-clusters are the seat of the very common process of calcification in the arachnoid membrane, and the cell-cluster should be considered to be the primary change in the membrane, permitting subsequent degeneration and infiltration with calcium. On the other hand, in certain of the series of cats described, a much more intensive proliferative process had taken place in the meninges, to result in the formation of typical endotheliomata.

The evidence indicates that certainly, in at least some of the cases, these new-growths represent similar but much more hyperplastic reactions of the same arachnoid cells than are involved in the formation of the much smaller, more slowly growing arachnoid cell-cluster. The exact cell-origin of such new-growths could not of course be told with exactness, but many features of similarity in the two types of growth suggest that this true new-growth is the proliferative end-result of the arachnoid cell-cluster while the very frequent process of calcification in these cellular nodules represents the degenerative.

The significance of the very slowly growing arachnoid cell-clusters must remain somewhat speculative. Their invariable occurrence in the older cats suggests that this cell-overgrowth resulting in the formation of such cell-clusters is merely a phenomenon of senescence. The cell-clusters are found quite frequently in adult animals, in which the evidences of old age are not present; they have not been found in young animals. This age-condition seems quite similar to that described by Goodpasture and Wislocki<sup>12</sup> in their paper "Old Age in Relation to Cell-Overgrowth and Cancer." In their series of 15 senile dogs, tumors were found in all of the animals, usually in more than one place (most frequently in liver, spleen and adrenals). The uniform and coincident occurrence of these tumors, and a certain similarity in the mode of formation and growth, indicated a common causative agent. If senescence be assumed to be this common causative agent, the cell-clusters of the arachnoid may well be classed in the same category.

The almost invariable occurrence of the arachnoid cell-clusters in animals of advanced age makes one hesitate to class them as abnormal structures but rather consider them as normal structures developed in senescence. In favor of classifying the structures as pathological are the evident hyperplasia of the normally flattened arachnoid cells, the tendency of the cell-cluster to show signs of calcification and the suggestive relationship of these nodules to endotheliomata. On the other hand, the inevitable occurrence of these cell-clusters in old animals leads one to the idea that, if not a normal change, the slowly progressing overgrowth must be viewed as a constant change in senescence. Calcification in the choroid plexus and epiphysis cerebri has been considered to be so frequent as to be practically a normal phenomenon of advancing age by Virchow,<sup>13</sup> certainly in such a degenerative process cell-changes must have preceded the actual degeneration. It seems most fair to look upon the arachnoid cell-cluster as an overgrowth of the arachnoid mesothelium, conditioned by the age of the animal and representing an almost inevitable alteration of advancing age.

#### CONCLUSIONS

The arachnoid mesothelial cells are normally of a low flat type but their morphology depends upon the particular physiological state of the cells at the time of examination. Under the stimulus of particulate matter and in acute infections, the cells increase in size, become phagocytic and at times form free-moving macrophages. Other changes in the growth of the

arachnoid cells lead to the almost invariable formation, in the older animals, of cell-clusters,—slowly progressive overgrowths, at times undergoing calcification and less frequently seemingly related to the formation of endothelioma. Hence, the morphology of the cells of the arachnoid may be said to depend not only upon the location of cells (as on the membrane or in an intradural cell-column) and upon the physiological state of the cells (as under the stimulus of particulate matter and infections), but upon the age-condition of the animal (as in the arachnoid cell-cluster).

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#### DESCRIPTION OF FIGURES

Fig. 1. Photomicrograph of section of arachnoid membrane covering posterior portion of left lateral sulcus of brain of old cat, showing thickening of mesothelial cells to form arachnoid cell-cluster. Above the membrane is the subdural space; below, the arachnoid trabeculae appear traversing the subarachnoid space. ( $\times 210$ )

Fig. 2. Photomicrograph of section similar to that of Fig. 1, but taken from anterior portion of lateral sulcus of same animal. A similar arrangement of arachnoid membrane with cell-cluster is given. ( $\times 120$ )

Fig. 3. Photomicrograph of section of arachnoid membrane covering left sylvian fissure, from same cat as those of Figs. 1 and 2. A typical arachnoid cell-cluster is illustrated; on the right the demarcation from the thin membrane is sharp, while on the left the swelling is continued somewhat diffusely into the membrane. ( $\times 120$ )

Fig. 4. Photomicrograph of section of arachnoid membrane (over right parasympathetic fissure) from brain of rather old but vigorous adult cat. Above is the dural surface of the membrane; the characteristic cell-cluster is shown lifted out in part from its depression in the membrane. Mesothelial strands attaching arachnoid to dura mater lie free in the subdural space. ( $\times 190$ )

Fig. 5. Photomicrograph of section of leptomeninges and brain (posterior portion of left parasympathetic gyrus) of an obviously old cat. In the midst of a typical arachnoid cell-cluster is an area of more or less homogeneous material; this area of degeneration shows no evidence of infiltration with calcium. ( $\times 120$ )

Fig. 6. Photomicrograph of section of arachnoid membrane over left lateral sulcus, from brain of same animal pictured in Fig. 5. The right half of the arachnoid cell-cluster here shown has undergone degeneration—in part of a homogeneous character—but elsewhere a beginning infiltration with calcium is evident. ( $\times 120$ )

Fig. 7. Photomicrograph of section of arachnoid membrane and brain (right parasympathetic gyrus) from an obviously old cat. The arachnoidal cell-cluster exhibits, in addition to several small and irregular calcareous deposits, typical spherical calcified bodies. Around certain of the calcareous nodules whorl-formation in the mesothelial cells is indicated. ( $\times 55$ )

Fig. 8. Photomicrograph of section of arachnoid membrane (anterior portion of left anterior sulcus) of brain of same animal as in Fig. 7. A large calcified body is shown on the left side of the arachnoid cell-cluster with no evidence of cell-reaction around it; in the remainder of the cell-cluster areas of beginning calcareous infiltration may be made out. ( $\times 120$ )

Fig. 9. Photomicrograph of section of leptomeninges and brain (coronal sulcus) of obviously old and weakened cat. Above in the leptomeninges is shown an early, well localized endothelioma with typical cell-whorls and calcified bodies. ( $\times 38$ )

Fig. 10. Photomicrograph of section of dura and tumor-mass from brain (left sylvian fissure) of obviously old cat. The tumor is a typical endothelioma and is intimately attached to the dura, which appears above. ( $\times 40$ )

Fig. 11. Photomicrograph of section of dura and tumor from brain (displacing right marginal gyrus) of same animal as that from which Fig. 10 is taken. Above is shown the dura of the falx cerebri, with the diverticula of the superior sagittal sinus. The typical "dural endothelioma" with its cell-whorls and calcareous bodies is intimately connected with the dura of the falx. ( $\times 52$ )

Fig. 12. Photomicrograph of section of tumor mass taken from brain in same region as that given in Fig. 11. A large cellular whorl, capped on the left by a crescent of calcareous material, is shown in the center of the photomicrograph; localized cell-whorls occur in the midst of the large whorl. ( $\times 40$ )



FIG. 1.



FIG. 2.



FIG. 3.



FIG. 4.



FIG. 5.



FIG. 6.



FIG. 7.



FIG. 8.



FIG. 9.

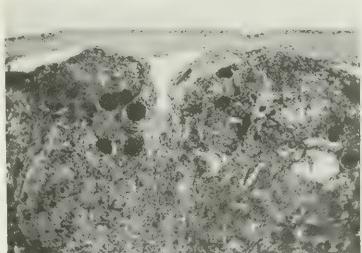


FIG. 10.

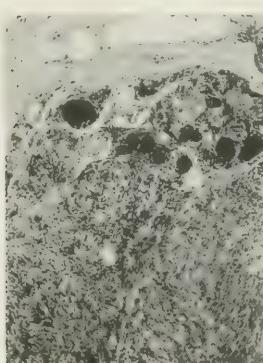


FIG. 11.

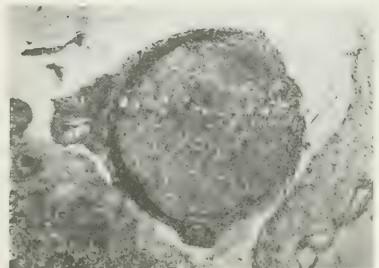


FIG. 12.



# A NOTE UPON THE OCCURRENCE OF CONGENITAL ATRIO-VENTRICULAR DISSOCIATION

## REPORT OF A CASE OF CONGENITAL COMPLETE HEART BLOCK

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It is an extremely interesting fact that although the number of cases of heart block, either congenital or acquired, occurring in childhood reported in the literature are comparatively few, the authentic instances of congenital partial or complete atrio-ventricular dissociation, in which the diagnosis has been established by graphic records, number but seven. All of these, with the single exception of the case reported by d'Espine,<sup>1</sup> have been found in association with congenital malformation of the heart. It is thus apparent that in spite of the relatively high incidence of congenital heart disease the occurrence of defects involving the conduction system and the presence of heart block associated with congenital malformation are infrequently met with.

In determining the exact etiology of the bundle defect in cases of heart block of assumed congenital origin, it is not within the limits of absolute accuracy to state positively that the lesion present existed at birth, but in the absence of any history of a possible post-natal infection and with the evidence of clinical congenital heart disease such a conclusion seems warranted. In this connection it is well to remember that it is extremely rare to find pathological changes dependent upon post-natal infections before the fourth or fifth year, and that the three great sources of endocardial and myocardial disease in childhood are, in the order of their gravity, rheumatic fever, scarlet fever and diphtheria; the first two involving both the valves and myocardium, the latter essentially the myocardium alone, so that in the absence of any history of these infections in the presence of cardiac disease, at least up to the age of four or five, the assumption of the congenital nature of the disease is wholly justifiable. It should further be emphasized that all evidences of cyanosis and clubbing of the fingers may be absent even with conspicuous congenital lesions.

Because of the uncertainty of the diagnosis in the absence of graphic records we have not included with the seven cases referred to above five cases of atrio-ventricular block occurring in childhood probably congenital in origin but not definitely established as such; two reported by Morquio,<sup>2</sup> one by von Starck,<sup>3</sup> one by Gill<sup>4</sup> and one by Zahorsky.<sup>5</sup> The case reported by Gill in a child of six, and regarded by him as a congenital heart block, had a ventricular rate varying between 47 and 60, and though the report is accompanied with respiratory and radial tracings the absolute confirmation of a radial and venous tracing is lacking.

In their article upon heart block in children Eyster and Middleton<sup>6</sup> tabulated the cases previously reported, with the exception of Gill's, including both congenital and acquired,

adding a case of their own. In this series these writers have included the case reported by van den Heuvel,<sup>7</sup> which we include in the seven cases of congenital heart block referred to above, but to which it is possible that exception might be taken on the basis of a strict interpretation of our title. The individual the subject of v. d. Heuvel's report was 23 years of age when first seen by himself and it was not until her 15th year that the slow cardiac rate was first noticed by a physician, though the history of the syncopal attacks dated from her second year. In view, however, of the detailed history as given, there can be no doubt, it seems to us, as to the congenital nature of the lesion in this case.

Upon the same ground of advanced age and in the entire absence of any definitely known early data, though with no history of rheumatic fever, chorea, scarlet fever or diphtheria, we have not included with the authentic cases the instance of complete atrio-ventricular dissociation associated with congenital pulmonary stenosis in a woman of 27 reported by one of us in an earlier communication.<sup>8</sup>

The previously reported cases of congenital atrio-ventricular dissociation, in which the diagnosis has been confirmed by graphic records, may be summarized briefly as follows. The case recorded by Fulton, Judson and Norris<sup>9</sup> in a child aged 22 months, with a ventricular rate of 42 to the minute, first noticed at the age of seven days, with a hypertrophied heart and a loud systolic murmur, from whom the polygraphic tracings showed an undoubtedly complete heart block. Wipham's<sup>10</sup> two cases, one baby of 18 months with a ventricular rate of 56 to 64, with a slight cardiac hypertrophy and a loud systolic murmur interpreted as due to a patent interventricular septum, from whom the electrocardiographic records showed a 2:1 block. The second case, a child of 12 years with a ventricular rate varying between 40 and 64, with an enlarged heart and a systolic murmur of maximum intensity in the fourth interspace near the sternum, with no cyanosis or clubbing of the fingers, from whom the electrocardiographic tracings showed an a-v block varying from 2:1 to a 3:1 rhythm with at times a complete dissociation.

The first of these children was admitted to the hospital suffering from whooping cough and bronchitis, and later developed a nasal discharge that proved to be of a "diphtheritic nature." In spite of this factor in the history the early clinical evidence of a very slow heart rate and the evidence of congenital heart disease would seem to justify the conclusion as to the congenital nature of the lesion. As to the second case, there may well be a reasonable doubt concerning the etiology of the

lesion since the slow heart rate was not noticed until the sixth year and there is the further history of an attack of measles "at an early age"; the exact date is not given. On the other hand, the clinical evidence of congenital heart disease, with the absence of all history of any illness but the attack of measles, favors the view that the cardiac lesion was congenital.

D'Espine (*loc. cit.*) has reported an instance of complete heart block in a boy of eight, regarded as undoubtedly congenital, and characterized by a single syncopal attack, with a slightly hypertrophied heart but no cyanosis or clubbing of the fingers, in whom there was present a soft systolic murmur interpreted as of extra-cardiac origin. This is the single instance of heart block in the literature believed to be not dependent upon acquired cardiac disease and not associated with congenital malformation of the heart. It is interesting that the child had a positive Wassermann reaction but no stigmata of

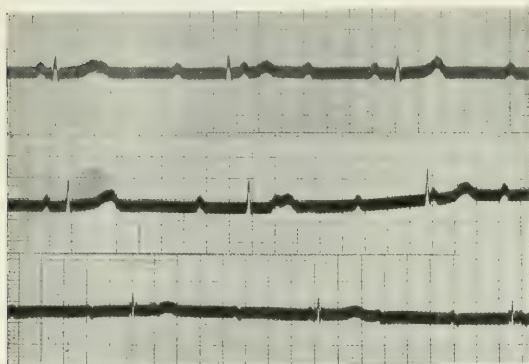


FIG. 1.—May 25, 1919. Complete atrio-ventricular dissociation. Atrial rate 103; ventricular rate 37. Note the absence of any evidence of ventricular preponderance.

hereditary syphilis. Graphic records showed a complete a-v dissociation, with an auricular rate of 10 $\frac{1}{2}$  and a ventricular rate of 26 to the minute, unaltered by atropine.

The case reported by van den Heuvel (*loc. cit.*) in a woman of 23, which in view of its long duration and the clinical history of repeated syncopal attacks is of unusual interest. At birth the child is said to have been conspicuously cyanotic, but apparently nothing abnormal was noted until her second year when the first syncopal attack occurred, lasting but a few moments. Following this she remained well until her sixth year, during which she had three syncopal attacks. There is a history of measles at eight, following which syncopal attacks again occurred. She then remained well until her 15th year. Similar syncopal attacks occurred in her 18th, 20th and 22d years, characterized by loss of consciousness and cyanosis but without convulsions. There was slight cyanosis of the extremities, an enlarged heart with a ventricular rate of 34 to the minute and a harsh systolic murmur of maximum intensity in the third left interspace. The clinical diagnosis was patent interventricular septum with slight pulmonary stenosis. Graphic records showed a complete a-v dissociation.

The case reported by Bass<sup>12</sup> was in a boy first seen at the age of 15 years and who also had a history of a mild attack of pneumonia at three and measles at five, in whom the slow cardiac rate, 37 to the minute, was first noticed at the age of 13. There was a slightly enlarged heart with a short blowing systolic murmur at the apex and a very rough systolic murmur of maximum intensity over the third left interspace and transmitted downwards, for a short distance, but not upwards. The lesion was interpreted as pulmonary stenosis. There was no cyanosis and no clubbing of the extremities. Electrocardiographic tracings showed the presence of an alternating 2:1 rhythm with a complete dissociation.

Finally the case reported by Rosenson<sup>13</sup> in a girl of 10 years who first came under observation at the age of eight, with a cardiac rate of 44 and without any other symptoms than a complaint of slight pain and distress over the precordium following exertion. There was no cyanosis. The heart was slightly enlarged. There was a long sawing diastolic murmur heard over the precordium, of maximum intensity in the second left interspace. The murmur was considered to be due to a congenital malformation because of its character and the history of the case. The defect was believed to be a direct communication between the aorta and pulmonary arteries just above the aortic valves. Electrocardiographic tracings—no figures are published—showed a complete a-v dissociation.

To the above cases we wish to add the following instance of congenital complete atrio-ventricular dissociation occurring in a girl in whom the exact diagnosis made at the age of three has been repeatedly confirmed by graphic records.

#### CLINICAL REPORT

K. W. Born Nov. 16, 1909. First seen March 11, 1915. Aged 5 years. Diagnosis: congenital malformation of the heart and congenital heart block.

F. H.—Negative.

P. H.—Third of four children, others well. Weight at birth between 9 and 12 pounds. Nursed six months and did well. Mother thinks that she had rather a blue look around the mouth and had a blue vein very prominent across the nose. At nine months she had bronchitis and it was noticed at this time that she had a cardiac murmur. At about two years of age she was seen by Dr. Walter James, who also confirmed the presence of a murmur, and a year later, when she was three, he saw her again and had electrocardiographic records taken which showed the presence of a complete heart block. In the summer of 1914 she had a slight syncopal attack and was seen by Dr. Gannett, of Boston, who also confirmed the diagnosis of heart block. She has never been short of breath, never cyanotic and has never had any evidences of an impaired myocardium. Recently she has played about just as any other child would do and there has been no more shortness of breath or cyanosis than would be seen with a perfectly normal child.

S. P.—The child is moderately nourished, rather spare and of good color. There is no cyanosis, dyspnea, changes in the gums or enlarged viscera.

Heart.—The apex beat is in the fifth interspace 8.5 cm. to the left of the mid-sternal line. Very slightly enlarged to the left. Rate very slow, 23 to the half minute. The sounds are clear, except for a rather rough and harsh systolic murmur of maximum intensity near the apex, not transmitted. The third heart sound is very plain. It is obvious from the venous pulsations

in the neck that there are two or three times as many auricular as there are ventricular systoles. The pulse is of good quality, regular and very slow. Electrocardiographic records were taken and the diagnosis of complete atrio-ventricular dissociation confirmed. Roentgenograms were also taken.

Seen again January 29, 1916. She had pertussis from June until September, 1915. Since then she has been very well. She has grown and gained in weight. Weight now 46 pounds and 6 ounces. Color good. She does not get short of breath even when running, but complains of an occasional "stitch in her side." Pulse 44 to the minute. Apex beat as noted above. Heart very slightly enlarged to the right. There is a harsh but somewhat blowing murmur which is heard over the precordium from the apex nearly to the base, but further to the left than is usually the case with open interventricular septal murmurs. The second pulmonary sound is accentuated. No auricular sounds heard. No pulmonary signs.

Seen March 6, 1917. Weight 54 pounds and 12 ounces. Height 50½ inches. She has been very well. No illness of any kind except a mild attack of otitis media which healed promptly after incision. No dyspnea. No cyanosis. The murmur is certainly much fainter than formerly, can hardly be heard when the child is standing or sitting up. It becomes more audible when she is lying down. Cardiac outline as previously noted. Ventricular rate 48 to the minute.

Seen May 25, 1919. She has developed very well. Present weight 74 pounds and 10 ounces. Height 4 feet 7 inches. Her color is good. She is able to skate 20 blocks on roller skates without any difficulty or distress. Occasionally she has what is called a "tired day" when she is glad to stay quiet, but these are infrequent. The apex beat is in the fifth interspace 8.5 cm. from the mid-sternal line. There is rather a rough short systolic murmur heard all over the precordium. The first sound is usually not very loud. From time to time, however, there is a marked accentuation of this sound. The heart rate is slow, 48 to 52 to the minute. From time to time a very characteristic third heart sound is audible. The cardiac outline seems no larger relatively than it was before. Electrocardiographic tracings taken at this time show a complete atrio-ventricular dissociation. Auricular rate 103, ventricular rate 37 to the minute. (See Fig. 1.)

The following interesting points brought out by this history may be emphasized briefly: The early diagnosis of the cardiac murmur at nine months of age, an evidence of the existence of congenital malformation of the heart, and the confirmation of the clinical diagnosis of heart block by electrocardiographic records at the age of three, the history of having passed suc-

cessfully through an attack of pertussis lasting four months in 1915, and the child's present normal appearance and ability to play and romp as any normal child.

When last seen in May, 1919, the very striking occasional accentuation of the first sound of the heart was a conspicuous feature and was interpreted as being due to the synchronous systole of auricle and ventricle, although the auricular systole falling in the long diastolic pauses could not be made out.

Perhaps the most significant feature of this small series of cases is the absence of any history of grave syncopal attacks except in the instance reported by v. d. Heuvel, which with one exception had the lowest ventricular rate, a fact in strict accordance with the physiology of the idio-ventricular rhythm. In cases 4 and 8 of our table there was a history of one syncopal attack of very mild type. It would seem apparently that as a result of the congenital nature of the lesion the heart early acquired the power of adapting itself to the constant load necessary to maintain an efficient circulation.

It is greatly to be regretted that we were unable to carry out an observation of the response to atropine, but in view of the long duration of the definitely known block there can be no question as to its organic nature. After exercise and under vagus stimulation there was no appreciable change in the ventricular rate recorded by the galvanometer.

#### EMBRYOLOGICAL DEVELOPMENT

Considering the nature of the development defect, it is apparent that the lesions associated with disturbances of conduction are, in the recorded cases, entirely confined to defects involving the main stem rather than one of its branches. It is also evident that the structural malformation involving the proximal region of the main bundle must occur at a very early period of embryonic development, possibly at that time when the first evaginations of the interventricular cavities take place at about the fourth week after fertilization. We know that the evolution of the His-Tawara bundle results from the growth downwards of the primitive cardiac tube, forming the ventricular cavities and interventricular septum, gradually severing all muscular continuity between auricles and ventricles,

TABULAR REVIEW OF CASES

Case No.	Author	Sex	Age	Age at time of first observation of slow cardiac rate	Hypertrophy of the heart	Interpretation of the cardiac murmur	Nature of the A-V dissociation	Ventricular rate	History of syncopal attacks	Presence or absence of cyanosis	Presence or absence of clubbing of extremities	Symptoms complained of
1.	Fulton, Judson and Norris. Wipham.	M.	22 months.	7 days.	Slight.	Patent interventricular septum.	Complete.	42	None.	Absent.	Absent.	None.
2.	F.	18 months.	18 months.	Slight.	Patent interventricular septum.	Partial 2:1 rhythm.	56-64	None.	Absent.	Absent.	None.	
3.	Wipham.	F.	12 years.	6 years.	Marked.	Patent interventricular septum.	Complete.	40-64	None.	Absent.	Absent.	Pain around the heart on exertion.
4.	d'Espine.	M.	8 years.	8 years.	Slight.	Extra cardiac.	Complete.	20-32	One attack.	Absent.	Absent.	None.
5.	van den Heuvel.	F.	23 years.	15 years.	Marked.	Patent interventricular septum.	Complete.	34	Present.	Slight.	Absent.	Syncope attacks.
6.	Bass.	M.	15 years.	13 years.	Slight.	Not definitely stated.	2:1 and complete.	37	None.	Absent.	Absent.	Dyspnea and palpitation on exertion.
7.	Rosenzon.	F.	10 years.	8 years.	Marked.	Communication between aorta and pulmonary artery just above aortic valves.	Complete.	44	None.	Absent.	Absent.	Pain and distress around the heart on exertion.
8.	Present case.	F.	10 years.	3 years.	Slight.	Patent interventricular septum.	Complete.	37	One attack at 4 years.	Absent.	Absent.	Occasional "stitch in the side."

except for a narrow strand that persists and is later differentiated as the atrio-ventricular bundle. It is readily conceivable that abnormal development at this time may involve only that group of cells which later is to become the a-v node or upper part of the main stem to a widely varying degree.

In view of the definite relationship existing between the main bundle of the conduction system and the interventricular foramen as shown by Keith,<sup>1</sup> it is interesting that more frequent disturbances of the conduction system are not met with. But, as pointed out by Keith, the a-v bundle is developed in the upper margin of the septum which represents a part of the lumen of the primitive heart. May not this fact explain its frequent escape from injury in these cases of congenital patent interventricular septum?

#### SUMMARY

To the seven definitely proven instances of congenital malformation of the conduction system of the heart we add another, making eight such cases in which the diagnosis has been confirmed by graphic records.

## ONE FACTOR IN THE MECHANISM OF HEMOLYSIS IN HEMOLYTIC ANEMIA

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The different types of anemia fall into three general groups; those due to blood loss, those due to faulty production of red blood cells either quantitative or qualitative, and those due primarily to increased destruction of the red blood cells in the body. This study is concerned with the anemias of the last group, the so-called hemolytic anemias, seen characteristically in two clinical conditions, primary pernicious or Addisonian anemia and hemolytic icterus.

The causes of the abnormal destruction of red blood cells in the hemolytic anemias are not yet established. The studies of Faust and Tallqvist on the anemia of *Dibothriocephalus latus* infestation,<sup>1</sup> of Iwao on the results of p-oxy-phenylethylamin (or tyramin) injection,<sup>2</sup> of Bunting<sup>3</sup> and of others, afford evidence that a blood picture such as is seen in Addisonian anemia may result from the action of a chemical hemolysin in the body. In the so-called hemolytic anemias efforts to prove the presence of a foreign hemolytic agent have not been successful. This evidence, however, is not necessary to prove the hemolytic character of the hemolytic anemias. If our understanding of fat digestion and absorption is correct, there is normally in the blood a sufficient amount of powerful hemolytic agents in the form of soluble soaps to explain the phenomena observed, provided they are free to act as hemolysins. Studies on these normal circulating hemolysins to determine whether they are increased in amount or altered in form in the hemolytic anemias have not been conclusive.<sup>4, 5, 6, 7</sup> If the hemolysis in the hemolytic anemias is not due (1) to the presence of a foreign hemolysin

We have been unable to find any report of a histological study of any of these cases.

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or (2) to an increase in the hemolysins normally present, another possibility that suggests itself is (3) some disorder in the mechanism that normally prevents the hemolytic substances present in normal individuals from acting as hemolysins.

It has not been definitely established why the hemolytic agents present in normal blood do not hemolyse the red blood cells; but it has been shown repeatedly that serum has great power to protect washed red blood cells from hemolysis by many different agents. Thus Ford<sup>8</sup> demonstrated protective power in normal serum against hemolysis by the hemolytic ingredient of *Amanita phalloides*, Moss<sup>9</sup> against the isohemolysins of the human species, Sellards<sup>10</sup> against the hemolysis of bile and bile salts, and Moss and Barnes<sup>11</sup> against cobra venom hemolysis. Noguchi<sup>12</sup> and Liebermann<sup>13</sup> showed that normal serum had power to protect against hemolysis by sodium oleate, and later Lamar proved this protective power not only against hemolysis of red blood cells<sup>14</sup> but also against lysis of pneumococci.<sup>15</sup> In view of these facts it seems reasonable to suppose that the hemolytic agents present in the blood normally do not hemolyse because of the power of serum to protect red blood cells against hemolysis by such chemical agents. If for any reason this protective power against hemolysis were diminished the normal hemolytic substances present in normal amounts might act as hemolysins in the body. It is suggested, therefore, that the hemolysis occurring in the hemolytic anemias, since not proven to be due to the presence of a foreign

hemolysin or to an increase of hemolysins normally present, may be dependent upon a diminution of the protective power of the serum against hemolytic agents. To test this hypothesis experiments were undertaken to determine the degree of protective power against hemolysis exhibited by the serum of patients having a hemolytic anemia, of patients with other diseases, and of normal persons.

To study the protective power of serum, a series of test-tubes containing constant quantities of different dilutions of hemolytic agent was set up and a constant quantity of the serum to be tested was added to each of these tubes. This mixture was incubated and cooled, a constant quantity of guinea-pig corpuscles was added and incubation was continued. Each tube of the series in the titration contained:

(1) Desired dilution of hemolytic agent.....	2.00 c. c.
(2) Serum to be tested (diluted 1-20).....	0.25 c. c.
(3) Washed guinea-pig cells (7.5 per cent suspension) .....	0.25 c. c.
Total mixture .....	2.50 c. c.

For the hemolytic agent sodium oleate—"Merck's highest purity"—was chosen because it is readily soluble, is a powerful hemolytic agent, and one that may be supposed to be present more or less constantly in the body. Throughout all the experiments to be reported the sodium oleate came from the same two ounce bottle in which it was delivered. The preparation is a white powder. Of this 100 mgm. were dissolved in 100 c. c. of sterile normal salt solution and further dilutions were made from this 1 to 1000 stock solution. The solution when used was slightly opaque, this opacity becoming greater on standing and with manipulation. The hemolytic power of the soap solution diminishes with the increase in opacity. To ensure the same degree of hemolytic power of the soap solution in each titration the technique used in its preparation was always uniform. The soap powder was dissolved in the salt solution each afternoon for the titrations of the next day, the sterile container was stoppered with cotton and, to ensure uniform conditions, the solution was kept in the incubator over night. The further dilutions made from this 1 to 1000 sodium oleate solution were carried out just before setting up the titration. It was diluted with sterile normal salt solution according to Table 1 in such a manner that the dilutions obtained were four-fifths of the dilution desired in the final preparations.

Two cubic centimeters of each dilution were put in a separate one of a series of tubes. When the serum and guinea-pig corpuscles had been added to each tube the total volume was 2.5 c. c., hence the necessity of making dilutions of sodium oleate only four-fifths of the desired final dilution.

The patient whose serum was to be tested was bled either late the afternoon before or on the morning of the titration. To ensure serum free from hemoglobin the syringe and needle with which the venapuncture was done were washed with sterile normal salt solution after they had been boiled. The blood (1 to 2 c. c.) was introduced into a sterile test-tube, allowed to clot and within two hours of the venapuncture the clot was separated, the tube centrifuged and the serum re-

moved with a pipette. This was then immediately inactivated on the water-bath at 56° C. for one hour. If not inactivated, serum rapidly loses its protective power; if inactivated the protective power diminishes somewhat more slowly. Serum retains some protective power for a long time apparently, for one specimen six weeks old and covered with mould still showed some power to protect guinea-pig cells against hemolysis by sodium oleate. The variation in this protective power of serum on standing was very irregular,

TABLE I  
TO MAKE DILUTIONS OF SODIUM OLEATE

e. c. of 1-1000 sodium oleate solution	e. c. normal salt solution	=	Dilution giving r sulting	Dilution of sod. oleate in final preparation
.1	2.3		24,000	30,000
.1	2.7		28,000	35,000
.1	3.1		32,000	40,000
.1	3.5		36,000	45,000
.1	3.9		40,000	50,000
.1	4.3		44,000	55,000
.1	4.7		48,000	60,000
.1	5.1		52,000	65,000
.1	5.5		56,000	70,000
.1	5.9		60,000	75,000
.1	6.3		64,000	80,000
.1	6.7		68,000	85,000
.1	7.1		72,000	90,000
.1	7.5		76,000	95,000
.1	7.9		80,000	100,000
.1	8.3		84,000	105,000
.1	8.7		88,000	110,000
.1	9.1		92,000	115,000
.1	9.5		96,000	120,000
.1	9.9		100,000	125,000
.1	10.3		104,000	130,000
.1	10.7		108,000	135,000
.1	11.1		112,000	140,000
.1	11.5		116,000	145,000
.1	11.9		120,000	150,000
.1	12.3		124,000	155,000
.1	12.7		128,000	160,000
.1	13.1		132,000	165,000
.1	13.5		136,000	170,000
.1	13.9		140,000	175,000
.1	14.3		144,000	180,000
.1	14.7		148,000	185,000
.1	15.1		152,000	190,000
.1	15.5		156,000	195,000
.1	15.9		160,000	200,000

however, so in the titrations recorded the serum, when used, was always less than twenty-four hours old. If the venapuncture was done the afternoon before, the inactivated serum in a sterile, stoppered test-tube was kept in the ice-box over night. Just before the titration was set up, sufficient normal salt solution was added to the inactivated serum to make a 1 to 20 dilution. Of this 0.25 c. c. was added to each tube, thus diluting the serum ten times more (the final volume of fluid in each tube was 2.5 c. c.) so that in the final preparation the serum was present in a 1 to 200 concentration.

The suspension of guinea-pig cells used was always freshly prepared, because the resistance of guinea-pig cells to hemol-

ysis is markedly diminished on standing any length of time in salt solution. The morning of the titration guinea-pig blood was taken by cardiopuncture into a syringe washed out with 1.5 per cent citrate in normal salt solution after boiling, and containing one or two cubic centimeters of the same citrate solution. This blood was introduced into a sterile centrifuge tube containing sufficient citrate solution to prevent clotting, the cells were thrown down by centrifugation and washed three times in normal salt solution. With each preparation, the last time the cells were centrifuged, the process was continued at the same speed for exactly twenty minutes, the volume of cells read and salt solution equivalent to one third the volume of cells was added to them giving a 75 per cent suspension of cells. Immediately before the cells were added to the tubes of the titration, this 75 per cent suspension was diluted ten times and 0.25 c. c. of the resulting 7.5 per cent suspension was added to each tube, thus giving a 0.75 per cent concentration of cells in the final preparation.

The 0.25 c. c. of serum 1 to 20 was added to the tubes containing 2 c. c. of different sodium oleate dilutions and this was incubated in a water-bath for one-half hour at 37.5° C. and then allowed to cool at room temperature for the same length of time before the guinea-pig corpuscles were added. It will be noticed that during this time the serum was allowed to act on the hemolytic agent before the corpuscles were added, the sodium oleate dilutions were only nine-tenths of the dilutions recorded in the final preparation for each tube, and the serum was not 1 to 200 but 1 to 180. After this preliminary incubation and cooling of the serum plus sodium oleate, the guinea-pig corpuscles were added and incubation was continued in the water-bath at 37.5° C. for two hours. Every half hour during this period each separate tube was shaken gently but enough to ensure an even suspension of the corpuscles, and a reading of the degree of hemolysis was made. At the end of two hours the test-tube racks were removed from the water-bath, each tube was shaken again and the racks put in the ice-box for one hour. This permitted enough sedimentation to make a final reading of the presence and amount of hemolysis in each tube. The recorded results then appear as in Table II. The interaction of serum, sodium oleate and corpuscles may be greatly hastened or increased by a rise in temperature, or retarded by a fall; hence, to get comparative results it is necessary that the incubation be at the same temperature (37.5° C.) each time. Furthermore, the hemolysis will continue for many hours even in the ice-box, so the time at which the readings were made was constant. Hemolysis progressed so slowly at lower temperatures, however, that rarely after one hour only in the ice-box did it go beyond that seen after two hours' incubation; but the one hour permitted sedimentation and thus facilitated readings of the results. With some practice, however, accurate reading of hemolysis can be made without sedimentation. The tubes may not be centrifuged, for the corpuscles are so injured by the exposure to sodium oleate solutions that the trauma incident to centrifugation produces hemolysis even in the higher dilutions of

TABLE II  
TITRATION OF THE SERA OF SIX CHARACTERISTIC CASES FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SODIUM OLEATE SOLUTION

F. E. Normal Control.

Dilutions of sod. oleate	45,000	50,000	55,000	60,000	65,000	70,000	75,000	80,000	85,000	90,000	95,000	Control
Incubation $\frac{1}{2}$ hr.....	-	-	-	-	-	-	-	-	-	-	-	-
" 1 hr.....	+	+	-	-	-	-	-	-	-	-	-	-
" $\frac{1}{2}$ hrs.....	++	+	-	-	-	-	-	-	-	-	-	-
" 2 hrs.....	++	++	-	-	-	-	-	-	-	-	-	-
One additional hr. in ice-box..	++	++	-	-	-	-	-	-	-	-	-	-

R. K. Age 55. *Diabetes mellitus.* R. B. C. 5,064,000, Hb. 95%, W. B. C. 10,000, P. M. N. 61%.

Incubation $\frac{1}{2}$ hr.....	-	-	-	-	-	-	-	-	-	-	-	-
" 1 hr.....	-	-	-	-	-	-	-	-	-	-	-	-
" $\frac{1}{2}$ hrs.....	+=	-	-	-	-	-	-	-	-	-	-	-
" 2 hrs.....	++	++	-	-	-	-	-	-	-	-	-	-
One additional hr. in ice-box..	++	++	-	-	-	-	-	-	-	-	-	-

B. R. Age 20. *Typhoid fever.* R. B. C. 2,616,000, Hb. 55%, W. B. C. 5,600, P. M. N. 50%.

Incubation $\frac{1}{2}$ hr.....	-	-	-	-	-	-	-	-	-	-	-	-
" 1 hr.....	+	++	-	-	-	-	-	-	-	-	-	-
" $\frac{1}{2}$ hrs.....	++	++	++	++	-	-	-	-	-	-	-	-
" 2 hrs.....	++	++	++	++	-	-	-	-	-	-	-	-
One additional hr. in ice-box..	++	++	++	++	++	-	-	-	-	-	-	-

W. J. M. Age 50. *Carcinoma of bladder.* R. B. C. 1,806,000, Hb. 28%, W. B. C. 23,760.

Incubation $\frac{1}{2}$ hr.....	-	-	-	-	-	-	-	-	-	-	-	-
" 1 hr.....	++	+	-	-	-	-	-	-	-	-	-	-
" $\frac{1}{2}$ hrs.....	--	+-	-	-	-	-	-	-	-	-	-	-
" 2 hrs.....	+	++	++	-	-	-	-	-	-	-	-	-
One additional hr. in ice-box..	+	+	++	++	-	-	-	-	-	-	-	-

T. C. Age 59. *Pernicious anemia.* R. B. C. 1,584,000, Hb. 34%, W. B. C. 4,600, P. M. N. 56%.

Incubation $\frac{1}{2}$ hr.....	+=	-	-	-	-	-	-	-	-	-	-	-
" 1 hr.....	++	++	++	++	+=	+=	-	-	-	-	-	-
" $\frac{1}{2}$ hrs.....	+	+	+	+	++	++	++	++	+=	-	-	-
" 2 hrs.....	+	+	+	+	+	+	+	+	+	-	-	-
One additional hr. in ice-box..	+	+	++	++	++	+	++	++	++	-	-	-

D. W. Age 35. *Pernicious anemia.* R. B. C. 1,470,000, Hb. 43%, W. B. C. 4,800, P. M. N. 61%.

Incubation $\frac{1}{2}$ hr.....	-	-	-	-	-	-	-	-	-	-	-	-
" 1 hr.....	++	++	++	++	-	-	-	-	-	-	-	-
" $\frac{1}{2}$ hrs.....	+	+	++	++	++	-	-	-	-	-	-	-
" 2 hrs.....	+	+	+	+	+	+	+	+	+	-	-	-
One additional hr. in ice-box..	+	+	++	++	++	+	++	++	++	-	-	-

Symbols: (-) indicates no hemolysis.

(+) " beginning hemolysis.

(++) " partial hemolysis.

(++) " hemolysis almost complete.

(++) " complete hemolysis.

In the last column is the control tube of serum 1-200 and guinea-pig cell suspension 0.75% in normal salt solution.

the sodium oleate, when in much stronger solutions after sedimentation without trauma in the ice-box there is no hemolysis.

With each titration two controls were set up.

(1) A 0.75 per cent suspension of guinea-pig cells in the normal salt solution used was incubated and examined for hemolysis at the same time as the tubes containing both serum and hemolytic agent. This was always negative.

(2) With each serum tested a tube was set up containing the same amount of serum and guinea-pig cells as the tubes of the titration but containing no hemolytic agent, the contents of the tube being made up to the required volume, 2.5 c.c., with sterile normal salt solution. If the serum was inactivated this was always negative for hemolysis. Occasionally, however, if such a preparation was set up with serum that had not been inactivated, it showed a slight amount of hemolysis.

Having thus proved (1) that the guinea-pig cells and normal salt solution used and (2) that the guinea-pig cells and salt solution plus the serum to be tested, showed no hemolysis, it remained to be proved that the different degrees of hemolysis recorded depended on the amount of protective power of the serum and not on variations in either the hemolytic power of the sodium oleate or the resistance of the guinea-pig cells.

When experiments were undertaken to determine whether or not the sodium oleate solutions as made up from day to day exhibited a constant degree of hemolytic power, the preparations were set up in exactly the same way as in titrations for protective power of serum except that human instead of guinea-pig corpuscles were used and no serum was added, the contents of the tubes being made up to the required volume (2.5 c.c.) with sterile normal salt solution. A slight variation in results was found when corpuscles of different individuals were used.

	Highest dilution showing hemolysis
(1) F. E., normal.....	70,000
(2) C. G., normal.....	65,000

This finding, however, apparently is due to differences in resistance to hemolysis of cells of different persons, for titrations of cells of one person set up in triplicate on the same day all showed the same reading and when repeated on subsequent days with fresh sodium oleate solutions the same results were obtained.

(1) F. E. normal

	Highest dilution showing hemolysis
November 14 .....	70,000
November 15 (1) .....	70,000
(2) .....	70,000
November 17 (1) .....	70,000
(2) .....	70,000
(3) .....	70,000

(2) C. G. normal

	Highest dilution showing hemolysis
November 14 .....	65,000
November 18 (1) .....	65,000
(2) .....	65,000
(3) .....	65,000
November 19 (1) .....	65,000
(2) .....	65,000
(3) .....	65,000

(3) F. C. normal

	Highest dilution showing hemolysis
November 5 .....	70,000
November 18 (1) .....	65,000
(2) .....	65,000
(3) .....	65,000
November 19 (1) .....	65,000
(2) .....	65,000
(3) .....	65,000

The findings in the last case, F. C., which showed different figures for a titration on November 5 and those on November 18 and 19 suggest that in this instance there might have been some variation in the sodium oleate solution; but the constant findings in titrations on nearby days point more strongly to the possibility that the difference is due to a variation from time to time in the resistance of one person's corpuscles to sodium oleate hemolysis.

When the constancy of the sodium oleate solutions had been established, the resistance of guinea-pig cells to hemolysis was studied in exactly the same way. Guinea-pig cells are much less resistant to sodium oleate hemolysis than human corpuscles and considerable variation was found. Hemolysis occurred up to dilutions of 1-140,000 to 1-180,000. This wide variation in resistance of guinea-pig cells, unprotected by serum, to hemolysis by sodium oleate solutions occurred in cells taken from the same pig on different days. Thus, for the cells of the same pig:

Titration of	Highest dilution showing hemolysis
Dec. 8, 1919 .....	140,000
Dec. 10, 1919 .....	170,000

This was not due to repeated bleeding, because pigs bled for the first time or for several days in succession might show cells of low resistance; thus:

Cells of	Highest dilution showing hemolysis
Pig bled three days in succession.....	170,000
Pig bled for the first time.....	170,000

Or they might show a greater resistance; thus:

Cells of	Highest dilution showing hemolysis
Pig bled four days in succession.....	145,000
Pig bled two days in succession.....	155,000

The difference in the resistance of the guinea-pig cells to hemolytic agents is not so great, however, as these titrations would indicate. Two suspensions of the cells with widely different figures for the highest dilution showing a trace of hemolysis might have the highest dilution showing complete hemolysis the same. Thus:

Highest dilution showing	some hemolysis	complete hemolysis
(1) .....	170,000	110,000
(2) .....	140,000	110,000

It is further of interest that in the dilution 1 to 140,000 there may not be any more hemolysis in a suspension of cells showing some hemolysis to a dilution of 1 to 170,000 than in one in which this dilution, 1 to 140,000, was the highest in which hemolysis occurred. At any rate it is evident that the difference in resistance of the guinea-pig cells to sodium oleate solution was not great enough to influence the reading of the serum test as set up, for with cells from different guinea-pigs

showing a variation when unprotected by serum the same results were obtained when protected by the same serum.

Patient	4 times bled pig	Last tube showing hemolysis twice bled pig
Normal .....	55,000	55,000
Hemolytic icterus .....	75,000	75,000
Pernicious anemia convalescent .....	75,000	75,000

And again, the constant results obtained with known normal serum not only bears evidence of the constant grade of hemolytic power exhibited by the sodium oleate solution, but also of the regularity with which cells of different guinea-pigs act when protected by the same serum.

F. E. normal control	Titration of	Highest dilution showing hemolysis
	January 13, 1920.....	55,000
	February 21, 1920.....	55,000
	March 8, 1920.....	55,000
	March 22, 1920.....	55,000

Sodium oleate solution is a colloid and when it is used as the hemolytic agent reliable results in quantitative hemolytic experiments are difficult to obtain. In spite of the most extreme care always to use a uniform technique, irregularities were sometimes encountered which were difficult to explain. On one occasion no satisfactory titrations could be obtained over a period of two weeks. For two weeks previous to this the sodium oleate powder had been exposed inadvertently to the fumes of petroleum ether, but after one week in a different cupboard it again reacted satisfactorily. This may have been merely a coincidence. Variations in humidity seemed to influence the properties of sodium oleate solutions, for in very wet weather the preparations were somewhat more opaque in appearance and such solutions seemed to suffer a slight but definite diminution in hemolytic power as compared with the clearer solutions which were the rule at ordinary times. Because of such difficulties extremely critical examination of results was necessary. It was for this reason that readings on each series of titrations were recorded at four half-hour periods as tabulated in Table II. If there was any irregularity in the progression of hemolysis from one reading to another it was considered sufficient evidence to condemn the entire titration. Similarly, if the known normal serum included as a control in each day's series of titrations of unknown sera did not fall within the narrow limits established by titration of the serum of many normal persons, the results of the entire series were not accepted; and if the other controls indicated that there was something wrong with either the sodium oleate solution, the serum, or the suspension of guinea-pig cells, all the titrations of that day's series were repeated with fresh preparations.

Throughout the experiments recorded the glassware used was chemically clean and sterile. Sterile technique was observed except that no effort was made to sterilize the sodium oleate powder and after it was dissolved in the sterile normal salt solution the mixture was not autoclaved. After a trial of several methods of cleaning glassware that found most satisfactory for this work was suggested by Dr. W. M. Allen working in this laboratory. After use the glassware was washed several times in tap-water, no soap being used. It was then

immersed in weak ammonium hydrate for twelve or more hours, removed from this and washed thoroughly several times in hot tap-water. This was followed by washing in distilled water, after which it was dried at a low temperature in the hot air sterilizer with the door open. After cooling, the glassware was stoppered with cotton and sterilized in the dry sterilizer, care being taken to avoid charring of the cotton stoppers. Quantitative measurements were made with volumetric pipettes and for the finer dilutions non-certified 1 c.c. pipettes graduated in hundredths were used. The titrations were set up in ordinary Wassermann test-tubes, 10 x 100 millimeters.

Titrations of a constant quantity of human serum as outlined above against varying strengths of sodium oleate solution, guinea-pig corpuscles being used as indicator, produced interesting results. From an examination of Table III it

TABLE III  
RESULTS OF TITRATIONS OF SERUM OF NORMAL PERSONS FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SODIUM OLEATE

No.	Name	Blood group	Date	Highest dilution of sod. oleate showing hemolysis
1	K. M. D.	I	11/5/19	40,000
2	H. P.	II	7/25/19	50,000
3	A. L.	II	8/12/19	55,000
4	V. R. M.	II	8/14/19	50,000
5	F. D. C.	II	10/29/19	45,000
6	C. G. G.	II	10/29/19	45,000
7	C. S.	II	1/14/20	50,000
8	H. R. B.	II	3/2/20	55,000
9	C. H. C.	III	8/13/19	50,000
10	H. M.	IV	8/8/19	50,000
			10/8/19	55,000
11	H. M. C.	IV	9/24/19	59,000
12	D. M. S.	IV	10/31/19	50,000
13	E. L.	IV	1/16/20	55,000
14	W. M. A.	IV	1/19/20	50,000
15	F. A. E.	IV	8/6/19	55,000
			9/18/19	40,000
			10/16/19	40,000
			10/24/19	45,000
			12/11/19	45,000
			12/15/19	50,000
			1/13/20	55,000
			2/21/20	55,000
			3/8/20	55,000
			3/22/20	55,000
16	W. S.		1/23/20	45,000
17	H. F. R.		1/21/20	50,000

will be seen that normal serum, 1 to 200 in the mixture, protected guinea-pig cells from hemolysis by sodium oleate up to strengths of from 1 to 55,000 to 1 to 40,000 and that with normal serum hemolysis was never seen with dilutions of sodium oleate greater than 1 to 55,000. The same was true of a wide range of other diseases as presented in Table IV.

There were only a few among the sera of cases with different types of anemia tabulated in Tables V and VI that did not have a lowered protective power against hemolysis as evidenced by the fact that hemolysis occurred in dilutions greater than

1 to 55,000. If the anemias not Addisonian in type are considered separately, Table V, it will be seen that nine of the twenty-one cases showed hemolysis in dilutions of 1 to 75,000 or over. Five of these showed hemolysis in dilutions greater than 1 to 75,000 as follows: three in 1 to 80,000, one in 1 to 85,000, and one in 1 to 90,000.

To be compared with the results of titrations on sera of cases in Table V are those on sera of pernicious anemia patients appearing in Table VI. Among the eighteen cases of pernicious anemia so studied the serum of thirteen showed hemolysis at 1 to 75,000 or above. In nine of the thirteen cases the protective power of the serum was lowered sufficiently to permit hemolysis in dilutions 1 to 85,000 or above. With the exception of one case, the serum taken after splenectomy from a patient with hemolytic icterus, the only sera which permitted hemolysis in dilutions greater than 1 to 85,000 were those of pernicious anemia patients, and among the eighteen titrated there were five that went beyond this point. The serum of one case of pernicious anemia did not inhibit hemolysis of the guinea-pig corpuscles in sodium oleate 1 to 105,000.

The five cases among those appearing in Table V, cases of anemia not Addisonian in type, that showed hemolysis in dilutions of over 1 to 75,000 merit special discussion. They

were diagnosed (1) hemolytic icterus, (2) Banti's disease, (3) Hodgkin's disease, (4) cirrhosis of the liver, and (5) secondary anemia, cause undetermined.

1. The case of hemolytic icterus in a white man, fifty years old, has been under observation for years. On this admission he complained principally of weakness. He was emaciated and his skin was a pale yellow color. The spleen was much enlarged and the liver moderately enlarged. He had hemorrhoids. The Wassermann reaction was negative. The urine showed albumin but no bile or blood. There was always a positive test for urobilin. His blood on the last admission showed an anemia with a color index greater than one, (R. B. C.—2,752,000, Hb.—55 per cent), moderate anisocytosis and poikilocytosis, normal total and differential white blood cell count (W. B. C.—9000) and normal platelets. The resistance of the red blood cells to hypotonic salt solution was found markedly decreased on repeated examinations. There were 8.4 per cent reticulated red blood cells. As the patient's condition improved, the degree of anemia became less but the color index remained high. In this case the color of the skin and the high color index suggest by analogy that the anemia was due to a hemolytic process and the constant finding

TABLE IV

RESULTS OF TITRATIONS OF SERUM OF PATIENTS SHOWING LITTLE OR NO ANEMIA FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SODIUM OLEATE

No.	Name	Age	Wassermann reaction	Date	W. B. C.	P. M. N. %	R. B. C.	Hb.%	List tube showing hemolysis	Diagnosis	Remarks
1	J. M. McK.	64	Neg.	7-31-19	4,920	....	3,936,000	78	50,000	Arterio-sclerosis and hypertension, myocardial insufficiency. Auricular fibrillation. Bell's palsy.	
2	N. M.	22	Neg.	7-30-19	10,800	64.	4,792,000	85	50,000	Post-influenza anemia, chronic tonsillitis, dental caries.	
3	P. I.	37	Neg.	7-31-19	13,080	....	3,864,000	80	50,000	Acute arthritis of the knee, gonorrhoeal (?)	
4	J. G.	63	Neg.	7-30-19	8,200	66.2	4,960,000	90	55,000	Dorsal and lumbar spondylitis.	
5	C. H. L.	21	Neg.	7-11-19	18,500	S2.	4,782,000	90	55,000	Pulmonary infection right base, acute, not tbc.	
6	C. L. W.	37	Neg.	7-11-19	7,960	....	4,632,000	83	55,000	Arterio-sclerosis and emphysema. Myocardial insufficiency.	
7	T. S.	31	Neg.	8-9-19	7,600	....	4,996,000	100	50,000	Addison's syndrome, tbc, adrenal (?)	
8	W. C. B.	36	Pos.	8-9-19	8,800	62.	4,800,000	85	50,000	Luetic aortitis and aortic insufficiency; tubercles.	
9	C. J.	60	Neg.	8-12-19	8,000	....	4,480,000	70	55,000	Carcinoma of stomach.	
10	W. M.	30	Neg.	8-13-19	7,600	....	4,472,000	80	50,000	Chronic nephritis.	Very edematous. Bl. pr. 220/160.
11	A. W.	48	Pos.	10-22-19	10,600	69.1	4,632,000	77	55,000	Syphilis, aneurism of aortic arch.	
12	M. E. S.	60	Neg.	10-17-19	6,100	68.4	4,750,000	90	55,000	Carcinoma at head of pancreas.	
13	B. F. M.	27	Neg.	10-18-19	5,640	58.	5,072,000	90	55,000	Diabetes mellitus.	
14	D. W.	29	Neg.	9-23-19	6,000	72.4	4,976,000	100	50,000	Viscerophtosis.	
15	E. K. U.	59	Neg.	7-23-19	25,000	....	11,000,000	130	50,000	Polycythemia.	
16	T. McB.	21	Neg.	7-29-19	7,800	....	4,760,000	81	55,000	Chronic infectious arthritis, right knee.	
17	L. B.	71	Neg.	7-29-20	8,760	....	4,480,000	98	60,000	Diabetes mellitus; furunculosis, healing.	
18	S. O.	70	Neg.	1-23-20	12,450	72.	4,976,000	95	50,000	Carcinoma of liver.	
19	J. T.	49	Neg.	1-26-20	9,200	74.	5,344,000	90	55,000	Myocardial insufficiency, auricular fibrillation.	
20	F. P.	27	Neg.	1-26-20	.....	.....	.....	..	50,000	Dementia praecox.	Some pyramidal elements in case.
21	R. K.	58	Neg.	1-28-20	10,000	61.	5,064,000	95	50,000	Diabetes.	
22	M. E. P.	58	Neg.	2-2-20	11,200	72.	3,216,000	85	40,000	Obstructive jaundice, intense. Appears to be carcinoma.	
23	I. S.	36	Neg.	1-21-20	6,560	83.	4,632,000	70	45,000	Hypertension, achylia, cord symptoms. Complete recovery. Macrocysts in blood. Slightly increased fragility of cells.	
24	A. P.	72	Neg.	1-28-20	8,900	84.	4,544,000	94	60,000	Diabetes.	

of urobilin in the urine bears further evidence of this condition.

2. The case diagnosed Banti's disease, like so many others with this diagnosis, is under some uncertainty as to the true condition present. The patient, a white man thirty-nine years old, had had hematemesis and blood in the stools at fairly long intervals over a period of four years. In all there were sixteen moderately severe hemorrhages. The patient had been feeling weak and was anemic during this time and had had altogether five transfusions. About the time of the first hemorrhage he had noticed a tumor in the left upper abdominal quadrant and this had increased in size gradually during the four years before coming under observation here. On admission he was undernourished and anemic, there was papillary atrophy of the tongue, and the spleen was greatly enlarged. The liver was not enlarged. The Wassermann reaction was negative. An x-ray examination of the gastrointestinal tract was negative. The stool was normal. Urine examinations were negative except that urobilin was found present on two occasions. The blood on admission showed a moderately severe anemia with a low color index, (R. B. C. 3,024,000, Hb. 35 per cent), marked poikilocytosis and moderate anisocytosis, slight diffuse basophilia, a severe leucopenia, (W. B. C. 3,400), and moderate diminution of platelets. The

resistance of the red blood cells to hypotonic salt solution was normal and there were 1 per cent reticulated red blood cells. The Goodpasture fibrinolysis test for chronic hepatic insufficiency was negative.

3. The case diagnosed Hodgkin's disease had been under observation for five years. When first seen he had had swellings on the sides of his neck for some time. His spleen was palpable. During the last five years the patient had been treated extensively with radium and x-ray so that his glands had never become very large but his weakness and anemia had gradually increased. On this admission the patient complained of weakness, shortness of breath, and cough. He was found to be extremely emaciated and his skin a lemon yellow color. There was a moderate general glandular enlargement. There were evidences of a mediastinal tumor, râles scattered throughout the chest, and some fluid on the right side. The liver and spleen were not enlarged. There were external hemorrhoids. The Wassermann test was negative. The stool examination was negative. X-ray examination of the mediastinum revealed a mass located there. Urine examination showed a slight trace of albumin. The blood showed a very severe anemia with a color index greater than one (R. B. C. 1,624,000, Hb. 38 per cent), moderate poikilocytosis and marked anisocytosis, a normal total white blood cell count (W. B. C.

TABLE V

RESULTS OF TITRATIONS OF SERUM OF PATIENTS SHOWING SOME ANEMIA NOT ADDISONIAN IN TYPE, FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SODIUM OLEATE

No.	Name	Age	Wasser-mann reaction	Date	W. B. C.	P. M. N. %	R. B. C.	Hb. %	Last tube showing hemolysis	Diagnosis	Remarks
1	J. G.	55	+	9-12-19	9,800	81	2,100,000	41	60,000	Carcinoma of stomach.	
2	W. L.	45	-	9-10-19	7,600	75	3,020,000	40	50,000	Secondary anemia. Hemorrhoids.	
3	C. R.	51	-	8-20-19	12,800	81	2,720,000	18	65,000	Abdominal carcinoma-cæcum. Intense secondary anemia.	
4	S. P.	31	-	9-24-19	6,200	..	2,500,000	62	45,000	Aestivo-autumnal malaria.	
5	McC. D.	19	-	9-25-19	4,200	83	3,920,000	65	60,000	Pleurisy with effusion. Tbc. of spine, stentor and tibia. Secondary anemia.	
6	I. L. D.	55	-	9-30-19	9,000	68	2,864,000	48	65,000	Myocardial insufficiency. Chr. nephritis. Goitre.	
7	E. H.	38	-	10- 6-19	5,500	..	2,600,000	33	45,000	Myeloid leukemia.	
8	W. R. D.	34	-	10- 8-19	3,400	67	3,024,000	35	80,000	Banti's disease. Splenomegaly.	
9	S. B.	47	-	11-25-19	19,200	82	2,960,000	72	65,000	Combined sclerosis.	
10	J. R.	70	-	1-14-20	8,600	85	3,600,000	40	60,000	Metastatic carcinoma of bones, glands, liver, lungs, etc.	
11	A. T. W.	50	-	1-28-20	6,720	50	3,352,000	60	70,000	Congenital hemolytic jaundice.	Splenectomy Feb. 20, 1920.
				3-15-20	9,000	..	2,755,000	55	65,000		
				3- 2-20	10,800	..	3,125,000	53	90,000		
				2- 2-20	5,600	\$0	2,610,000	55	65,000		
				2- 4-20	3,610	..	3,184,000	52	75,000		
				2- 6-20	4,880	46.66	3,216,000	62	70,000		
				2-18-20	7,120	50	4,964,000	58	75,000		
									50,000		
13	A. W. F.	34	-	2- 6-20	3,600	65	2,620,000	40	65,000	Cirrhosis of liver. Cancer of liver (?)	
14	W. J. M.	50	-	2-16-20	23,760	..	1,896,000	28	60,000	Tumor of bladder. Secondary anemia.	Patient very ill.
15	J. R.	39	-	2- 16-20	3,340	64	1,992,000	29	70,000		
16	D. T.	47	....	2-18-20	5,320	61	1,880,000	27	80,000	Myomata uteri (submucous) necrotic.	
17	M. E. J.	48	-	2-23-20	21,560	..	.....	27	75,000	Cirrhosis of liver?	
18	A. W. V.	52	-	2-27-20	9,240	81	1,624,000	38	85,000	Late stage of Hodgkin's Disease.	
19	J. G.	..	....	3- 8-20	5,000	..	2,456,000	42	85,000	Primary aplastic anemia.	
20	E. J.	20	Doubtful.	1-19-20	840	..	1,200,000	29	75,000		
21	S. C.	23	-	10-14-19	6,200	..	3,890,000	76	65,000	Typhoid fever.	
										Were there nothing else to explain the blood picture it might have been P. A. Ct>1.	

9,240) with a slightly increased percentage of polymorphonuclear neutrophiles, and a moderately decreased number of platelets. The resistance of the red blood cells to hypotonic salt solution was normal. There were 2.2 per cent reticulated red blood cells. As the anemia improved, the color index came down to a little below one but was always high. The blood picture of this patient resembled that of pernicious anemia very much. It differed from it in that there was a higher total white count and percentage of polymorphonuclear neutrophiles than is usually seen in Addisonian anemia and the degree of poikilocytosis was less than is to be expected in an anemia so severe.

4. The case diagnosed cirrhosis of the liver was that of a woman forty-eight years old who had been ill for one year. She had been having abdominal pain, nausea and occasional vomiting, and acid eructations after meals. Her abdomen began to swell about one year before admission here and during this period she had been tapped four times. Recently her ankles had become swollen, she had had some shortness of breath on exertion and had suffered from intense thirst. She had noticed that her urine was scanty. When examined she was found to have fluid in her abdomen and edema of the lower extremities. The spleen was not palpated but was found enlarged on percussion. The liver could not be felt. There

were external hemorrhoids and dilated veins over the abdomen. The Wassermann test was negative. The stool was normal. The phenolsulphonephthalein excretion was normal. A test-meal showed nothing pathological. The urine was normal except that on one occasion sugar was found to be present. The blood was normal except for a moderate degree of anemia with a color index slightly less than one. (R. B. C. 3,796,000, Hb. 65 per cent, W. B. C. 7,080).

5. The case diagnosed secondary anemia was that of a man thirty-nine years old who had received a very severe blow on the right side of the body about one year before. He had had pain and shortness of breath at intervals since. On rare occasions he had spat blood. He had been unable to work since the injury. During the last few months he also had had some pain after eating, and sometimes three or four watery stools a day. When examined he was slightly dyspneic, was emphysematous, and very pale. The Wassermann test was negative. An x-ray examination of the gastrointestinal tract was negative. Examination of a test-meal was negative. The stool showed nothing pathological, notably no blood. The urine was negative. The blood showed a severe anemia with a color index greater than one, (R. B. C. 1, 540,000, Hb. 32 per cent, W. B. C. 7,070). As the anemia improved, the

TABLE VI

RESULTS OF THE TITRATIONS OF SERUM OF PATIENTS WITH ADDISONIAN ANEMIA FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SODIUM OLEATE

No.	Name	Age	Wassermann reaction	Date	W. B. C.	P. M. N. %	R. B. C.	Hb.%	Last tube showing hemolysis	Diagnosis	Remarks
1	H. H. C.	66	—	8-6-19	2,600	58	670,000	15	80,000	Pernicious anemia.	Hemolysis probably higher but tubes not run further. Has had three transfusions since last test. Patient very much improved. Discharged.
				9-2-19	4,100	40	1,000,000	24	75,000	.....	
				10-4-19	5,300	60	3,224,000	56	90,000	.....	
2	E. B.	43	—	10-16-19	9,800	.....	1,870,000	30	95,000	Pernicious anemia.	Transfusion five days ago. Since then patient feels much better. Transfusion March 18.
				10-27-19	7,000	..	1,720,000	35	80,000	.....	
3	J. G. P.	33	—	4-5-20	1,950	45	1,788,000	22	85,000	Pernicious anemia.	.....
4	J. V. P.	56	—	8-14-19	2,920	50	1,688,000	50	70,000	Pernicious anemia.	.....
5	J. A. H.	41	—	9-5-19	8,600	72	1,500,000	38	75,000	Pernicious anemia.	.....
6	S. C.	66	—	10-20-19	1,760	..	1,624,000	29	95,000	Pernicious anemia.	.....
				10-31-19	4,850	..	2,388,000	35	90,000	.....	Patient had tranfusion 3 days ago. Feeling better. Died Jan., 1920. Patient died 12 hours after serum was taken.
7	R.	..	....	10-11-19	.....	..	510,000	9	105,000	Pernicious anemia.	
8	M. G.	44	—	12-11-19	3,500	53.5	1,650,000	36	75,000	Pernicious anemia.	
9	T. E. C.	59	—	2-27-20	6,200	66	1,524,000	35	70,000	Pernicious anemia. Mitral stenosis.	Not certain patient does not have an active endocarditis. Active endocarditis seems very questionable. Patient not very ill.
				3-5-20	4,600	56	1,584,000	31	90,000	.....	
10	D. W.	35	—	8-5-20	4,800	..	1,470,000	43	85,000	Pernicious anemia.	.....
11	A. M.	30	—	3-5-20	10,000	55	1,770,000	45	85,000	Pernicious anemia.	Patient not very ill.
12	H. L. McW.	31	—	3-5-20	2,410	33	824,000	28	65,000	Pernicious anemia.	Transfusion (600 c. c.) 3 days ago.
				2-15-20	1,820	32	1,544,000	31	70,000	.....	
				2-23-20	2,440	34	1,632,000	40	70,000	.....	
13	F. T. H.	35	—	1-16-20	4,400	67	736,000	14	85,000	Pernicious anemia.	.....
14	F. L.	35	—	3-31-20	2,700	45	1,250,000	30	65,000	Pernicious anemia.	.....
15	S. F. M.	47	—	3-22-20	5,960	67	1,265,000	27	60,000	Pernicious anemia.	Patient has had no transfusion.
				3-29-20	5,680	65	1,198,000	27	70,000	.....	
				3-29-20	4,400	62	1,230,000	33	75,000	Pernicious anemia. Amoebic dysentery.	
16	B.	40	....	1-21-20	5,310	64	2,238,000	46	55,000	Pernicious anemia.	.....
17	S. E.	53	—	5-10-20	2,350	68	2,064,000	35	80,000	Pernicious anemia.	.....
18	R. E. W.	45	—	5-10-20	2,350	68	2,064,000	35	80,000	Pernicious anemia.	.....

color index became a little less than one but always remained high.

These cases have been presented in some detail because the anemia present was associated with other findings of special interest. It was not in any one of these five cases a frank secondary anemia as that due to the blood loss of hemorrhage or to myelopoietic hypofunction of infections or cachexias; nor was it the type of anemia due to disturbances of iron metabolism as in chlorosis and some anemias of children. The case of hemolytic icterus was a typical case, showed all the accepted evidences of an anemia due to blood destruction in the body, and may be considered a hemolytic anemia. Three of the four remaining cases had high color indices, two of them greater than one. The remaining case that had a low color index showed urobilin in the urine. The most interesting feature, however, is that in four of the five cases there were evidences of involvement of the spleen in the disease process. Except for hemolytic icterus, the exact status of those anemias associated with disorders of the spleen as in these cases has not been established; and the exact mechanism of the anemia seen in diseases involving the spleen has not yet been explained.<sup>10</sup> In this connection it is interesting to note that with one exception the only cases tabulated in Table V (cases of anemia not Addisonian in type) that showed marked diminution of pro-

To sum up the findings, among the sixty-two sera of normal people and of patients suffering from a wide range of diseases without anemia or with anemia not Addisonian in type presented in Tables III, IV, and V, there were only nine that showed hemolysis in dilutions of sodium oleate greater than

TABLE VIII

A COMPARISON OF THE PROTECTIVE POWER OF THE SERA OF ALL CASES OF ADDISONIAN ANEMIA WITH R. B. C. COUNTS OVER TWO MILLION WITH THAT OF THE MORE SEVERE SECONDARY ANEMIAS TESTED

## PERNICIOUS ANEMIA

Name	R. B. C.	Hb. %	Highest dilution of sodium oleate showing hemolysis
H. H. C.....	3,224,000	56	90,000
J. G. P.....	2,152,000	68	80,000+
S. C.....	2,388,000	35	90,000
S. E.....	2,236,000	46	55,000
R. E. W.....	2,064,000	35	80,000

## SECONDARY ANEMIA

Name	R. B. C.	Hb. %	Highest dilution of sodium oleate showing hemolysis	Diagnosis
C. R.....	2,720,000	18	65,000	Carcinoma of cecum.
J. G.....	2,100,000	41	60,000	Carcinoma of stomach.
S. P.....	2,560,000	..	45,000	Estivo-autumnal malaria.
E. H.....	2,600,000	38	45,000	Myeloid leukemia.
W. J. M. ....	1,896,000	38	60,000	Tumor of bladder.
G. R.....	1,992,000	29	70,000	Severe secondary anemia cause undetermined.
S. R.....	2,700,000	47	60,000	Metastatic carcinoma of bone.
G.....	1,290,000	20	75,000	Primary aplastic anemia.

TABLE VII

A. TABULATION OF THE NUMBER OF CASES ACCORDING TO THE HIGHEST DILUTIONS OF SODIUM OLEATE SHOWING HEMOLYSIS OF GUINEA-PIG CORPUSCLES IN THE PRESENCE OF THE RESPECTIVE SERA

- (1) Normal persons and patients showing no anemia—41 cases.
- (2) Cases of Addisonian anemia—18 cases.
- (3) Cases of other types of anemia—21 cases.

Dilutions of sodium oleate	45,000	50,000	55,000	60,000	65,000	70,000	75,000	80,000	85,000	90,000	95,000	100,000	105,000	Total
Cases with no anemia..	6	20	13	9	..	..	..	..	..	..	..	..	..	41
Cases of Addisonian anemia	..	..	1	..	1	3	3	1	4	2	2	..	1	18
Cases with other anemias	2	1	..	4	5	..	4	3	1	1	..	..	..	21

B. TABULATION THE SAME AS ABOVE EXCEPT THAT THE CASES SHOWING EVIDENCES OF INVOLVEMENT OF THE SPLEEN ARE INCLUDED WITH THE CASES OF ADDISONIAN ANEMIA

Dilutions of sodium oleate	15,000	20,000	30,000	50,000	60,000	65,000	70,000	75,000	80,000	85,000	90,000	95,000	100,000	105,000	Total
Cases with no anemia..	6	20	13	2	..	..	..	..	..	..	..	..	..	..	41
Cases of hemolytic anemia and spleno-megaly	..	..	1	..	1	3	3	4	5	3	2	..	1	23	
Cases with other anemias	2	1	..	4	5	..	1	..	..	..	..	..	..	..	16

tective power of the serum against hemolysis could be assigned to this group of cases without any hesitation. The type of anemia in the fifth case diagnosed secondary anemia, cause undetermined, with a color index greater than one, is difficult to determine.

1 to 65,000, and five of these have been specially discussed. Among the eighteen sera from cases of Addisonian anemia appearing in Table VI all but two showed hemolysis in dilutions of sodium oleate greater than 1 to 65,000, many of them in very much greater dilutions. These results appear in summary in Table VIIA. If those cases which are not pernicious anemia but are associated with conditions in which the spleen is involved in the disease process are included with the pernicious anemia cases, the results are very striking (Table VIIB).

That the amount of protective power exhibited by the serum was not dependent solely upon the degree of anemia, as contrasted with the type, is shown in Table VIII. Here all the cases of pernicious anemia with more than 2,000,000 red blood cells per cubic millimeter are compared with the more severe secondary anemias.

In Table IX the results of repeated titrations on one case of pernicious anemia are tabulated. From this it will be seen that the protective power of the serum fluctuated markedly, this to be compared with the relative stability of protective power of normal serum as exhibited by a normal

control, (Case 15, Table III). These fluctuations in the protective power of the serum in the case of pernicious anemia so studied were independent of changes in the blood picture. It was noteworthy, however, that when the titration of the protective power of the serum showed a value approaching normal, the patient felt better, and when the protective power was low, he seemed to be more ill. This is in line with the observations of all clinicians who have followed these cases closely, that the feeling of well-being of the patient or the reverse seems to be independent of his blood picture at the time. These fluctuations, apparently dependent upon the clinical

pernicious anemia the anemia is but one manifestation of a complex disease.

When this work was undertaken it was hoped that if any diminution in protective power of serum against hemolysis could be demonstrated in anemic conditions, it might prove to be a finding confined to Addisonian anemia and thus be of value as a diagnostic procedure in difficult cases. The five cases not pernicious anemias which showed hemolysis in the higher dilutions, and the several cases of pernicious anemia that do not show greater diminution in protective power than anemias of other kinds, make this method of study of little value in diagnosis. One explanation of the high protective values obtained in some of the pernicious anemia cases has been suggested; namely, the patients were in good condition when tested. The possibility should also be kept in mind, however, that the cases at present diagnosed "pernicious anemia" may include more than one disease and that this method of study may have differentiated them. Additional study is needed on this point. It is hoped that further study of the protective power of serum in various diseases, especially pernicious anemia, may show that the information afforded by this procedure is of value in prognosis, and will aid in determining when a transfusion is indicated. Transfusion may improve the protective power of the serum slightly or markedly, but always results in some improvement. Sometimes this improvement, as judged by the titration of the protective power of the serum, does not last; sometimes it becomes progressive.

#### CONCLUSIONS

From the results of tests made of the protective power of human serum against hemolysis of guinea-pig cells by sodium oleate certain conclusions may be drawn.

(1) The protective power of the serum of normal persons and of patients suffering from a wide range of diseases without anemia is remarkably constant in degree.

(2) In anemias of various types the protective power of the serum is diminished.

(3) This diminution is most marked in anemias which are hemolytic in character and in conditions in which the spleen is involved in the disease process.

(4) In pernicious anemia, the diminution of protective power of the serum is very striking, both in degree and the regularity with which it is found.

(5) The protective power of the serum in cases of pernicious anemia varies greatly, but seems to parallel more closely the general condition of the patient than the blood picture at the time the titration is done.

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TABLE IX

THE RESULTS OF REPEATED TITRATIONS OF THE SERUM FROM A PATIENT WITH ADDISONIAN ANEMIA FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SODIUM OLEATE

F. T. H. 35 years old. *Pernicious anemia*. Wassermann negative.

Date	W. B. C.	P. M. N. %	R. B. C.	Hb. %	Last tube showing hemolysis	Remarks
1/16/20	4,400	67	736,000	14	85,000	Transfusion 1/16/20 300 c.c.
1/19/20	3,400	..	848,000	20	70,000	Transfusion 1/17/20 300 c.c.
1/26/20	5,600	..	1,696,000	42	60,000	Transfusion 1/24/20 600 c.c.
2/2/20	10,800	70	1,880,000	43	50,000	
2/9/20	5,300	..	2,006,000	41	70,000	
2/16/20	3,400	57	1,872,000	44	70,000	Transfusion 2/13/20 600 c.c.
2/23/20	.....	..	.....	..	55,000	
3/1/20	3,600	64	2,832,000	56	75,000	Transfusion 2/26/20 600 c.c.
3/8/20	4,800	60	2,280,000	56	75,000	
3/15/20	4,600	71	2,285,000	55	60,000	
3/22/20	3,960	54	1,928,000	42	75,000	
3/29/20	3,080	45	1,690,000	34	80,000	Transfusion 3/29/20.
4/5/20	2,600	47	2,372,000	45	90,000	
4/27/20	3,000	49	1,272,000	27	100,000	
5/3/20	3,760	54	1,076,000	22	80,000	
5/10/20	1,960	35	586,000	13	90,000	
5/17/20	2,280	58	986,000	20	85,000	Transfusion 5/12/20.

condition of the patient, may explain the good titration values obtained for the sera of a few pernicious anemia patients titrated only once. This is borne out by the fact that of the four cases, Nos. 4, 12, 14 and 17, which showed sera with protective power very close to normal, three went into remission promptly, two of them without transfusions. Subsequent titrations on the one case that did not improve promptly, showed a diminished protective power in spite of the fact that he had received transfusions. The fact that improvement in the titration value runs more or less parallel with the way the patient feels and precedes the improvement in the blood picture strongly suggests that many of the general symptoms of the patient with pernicious anemia, if not directly due to the lowering of the protective power of the serum itself, may depend upon the same underlying cause rather than upon the degree of the anemia alone. This is tantamount to saying what has been apparent to clinicians for some time, that in

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## THE COAGULATION TIME OF CITRATED PLASMA ON RECALCINATION

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The determination of the coagulation time of the blood is of great importance in the haemorrhagic diathesis, and more especially—as Sahli's fundamental work has shown—for the diagnosis of haemophilia, which in sporadic cases may be somewhat difficult.

Having tried both the capillary methods (according to Wright's modification) and those based on an examination of larger amounts of venous blood, I have become convinced that these give very unreliable results.

The technique advised by Howell in 1914 may, with some alterations, give better results. The method consists in observing the coagulation time of optimally recalcinated oxalated plasma and is carried out as follows:

Four cubic centimeters of venous blood are mixed with 0.5 c. cm. of 1 per cent sodium oxalate and shaken. After centrifugation, 5 drops of the plasma are dropped into each of four small test-tubes; one then adds, respectively, 1, 2, 3 and 4 drops of .5 per cent calcium chloride to the tubes and rotates the stand 90° every minute till the liquid in one of the tubes stiffens.

Howell's determinations were carried out at room temperature and showed a coagulation time (prothrombin time) of about 10 minutes, a marked protraction being found only in hemophilia.

My object now has been to modify this procedure so that it might be carried out on citrated blood on the same specimen as used for counting the platelets by Oluf Thomsen's method.\*

The method is open to criticism for various reasons:

1. Most authors agree that the temperature has a decided influence on the coagulation time, whereas Howell uses room temperature, a very variable factor.

2. The conditions of the experiment are different from those naturally present in shed blood; consequently, the results cannot be compared.

3. The coagulation time depends upon the platelet content of the plasma which varies with the intensity of the centrifugation.

In the elaboration of the method of the following experiments I have tried to overcome these objections. My technique in brief is as follows:

An unsilvered half-liter Dewar (vacuum) flask is provided with a cork with five holes, one for a thermometer and four for the miniature test-tubes. Before the experiment the flask is filled with water at 37° C., which will then remain at a temperature between 37-33° C. for several hours.

About 4.5 c. cm. of blood are taken with a curved needle into a centrifuge tube divided into tenths of a c. cm. and containing .5 c. cm. of 10 per cent sodium citrate solution. after starting the stop-watch, 2, 3, 4 and 5 drops of 1 per cent sedimented—excepting in cases of polycythaemia—so as to allow one to draw off .1 c. cm. of plasma for each of the four miniature test-tubes which have previously been inserted into the holes in the cork of the Dewar flask.

The test-tubes must be kept scrupulously clean and must have an internal diameter of 9-10 mm. The right size may be selected with a Hegar dilator or some similar instrument.

One then adds, going from left to right, 8, 7, 6 and 5 drops, respectively, of physiological saline solution to the tubes, and, after starting the stop-watch, 2, 3, 4 and 5 drops of 1 per cent crystallized calcium chloride solution ( $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ ). Pipettes giving 20 drops to the cubic centimeter were employed.

Every thirtieth second the flask is then rotated to the horizontal position until at last the surface of the liquid in one of the tubes (generally the second or third) fails to move. The interval between the recalcination and the solid clotting of the optimally recalcinated glass is called the coagulation-time, though it marks neither the beginning of the coagulation, which may be observed half a minute earlier, nor the

\* Gram: Arch. Int. Med., Chicago, 1920, XXV, 325.

end. In normal cases, that is, in persons not suffering from haemophilia or platelet deficiency, the coagulation time is found to lie between 3 and 6 minutes inclusive.

The error on the determination is relatively slight since double specimens will show identical values or variations of one-half or rarely 1 minute and always within the said boundaries.

TABLE 1  
DOUBLE SPECIMENS

Name	Diagnosis	c.t. 1 min.	c.t. 2 min.
H. W.	Ulc. ventr.	4½	4
A. P.	Colitis	3½	3½
A. H.	Ulc. ventr.	4	4
N. S.	Diabetes	4½	4½
H. W.	Ulc. ventr.	3½	3½
K. P.	Vertigo	4	4
C. J.	Normal	4½	4½
J. A.	Iscias	5	5
S. C.	Normal	3½	3½
N. C.	Normal	4	4½
A. J.	Normal	5½	4½

The time elapsing after the taking of the blood is—within 5 hours—of no consequence, as shown in Table 2.

TABLE 2

OBSERVATIONS ON THE SAME SPECIMEN AT VARYING TIMES AFTER THE TAKING OF THE BLOOD

Name	Diagnosis	1 hour		3 hours		5 hours	
		c.t. min.					
A. J.	Obstipation	5½	5	..	..	..	..
K. K.	Pneumonia	5½	..	..	5½	..	..
A. H.	Ulcus ventr.	4	..	..	4	..	..
M. O.	Neurasthenia	5	4½	5	..	..	..
J. E.	Graves' disease	4½	4	4	4½	..	..
W. K.	Aplastic anaemia (platelet deficiency)	7½	7	..	..	..	..

The reasons for the technique selected are the following: Constant temperature is necessary (Addis and others). This is shown definitely by the experiments in Table 3, which gives the result in five cases at varying temperatures, larger blood specimens (20 c. cm.) being used to procure sufficient plasma. The advantage of observing the coagulation at 35° C. is obvious, since the variations in coagulation time due to a given change of temperature increase rapidly as the temperature becomes lower.

TABLE 3

INFLUENCE OF TEMPERATURE ON COAGULATION

Diagnosis	c.t. min.					
	15°	20°	25°	30°	35°	40° c.
Normal	15	9	4½	3½	3½	3½
Normal	15½	9	6½	5	4½	4½
Cardialgia	16½	11	5	4	4	3½
Ulc. ventr.	13½	9	5½	4	3½	3½
Neurasthenia	14½	9	6	4	4	4½

Mean values ..... 15 9.4 5.5 4.1 3.9 3.9

The use of the unsilvered vacuum flask ensures a constant temperature for hours, and obviates the necessity of extracting and cooling the tubes for inspection every thirtieth second.

In laboratories possessing a thermostat room the determinations may conveniently be carried out in this, thus doing away with the flask. The test-tubes used must be clean and have a constant size, since the coagulation time is a product of the innate qualities of the blood and its surroundings during the clotting.

The recalcination used is the result of experience which showed that the optimal recalcination always took place in the tubes containing 2, 3, 4 and 5 drops of a 1 per cent  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ . If instead of a 1 per cent a 3 per cent solution is used, the recalcination must be 1, 2, 3 and 4 drops. Cases of protracted coagulation time, where the optimal recalcination was 2 or 5 drops, were controlled afterwards with 1 or 6 drops, respectively, no errors being found.

The variations due to different recalcination are shown in Table 4.

TABLE 4

COAGULATION TIME VARIATIONS DUE TO DIFFERENT RECALCINATION

Name	Diagnosis	1	2	3	4	5	6	7	8	Drops
K. B.	Normal	10½	6	4½	4	5½	6½	8	7½	Min.
J. E.	Normal	7½	5½	4½	5	6½	..	..	..	Min.

It will be seen that too low recalcination is much more effective in lengthening the coagulation time. The addition of sodium chloride solution to make the volume uniform in all tubes seems not to be strictly necessary, though I have no experiments to prove it. The fibrinogen content does not influence the coagulation time, even very low values being sufficient to cause solid clotting. Determinations of the fibrin percentage have been carried out in all cases.

The method presented differs from the original one of Howell inasmuch as it uses the sedimentation plasma containing the platelets in stable suspension.

This may cause difficulties in healthy men with very high red cell counts; these, however, may be obviated by taking double specimens in such cases. The reason for doing this lies in the fundamental importance of platelets for the coagulation time.

By centrifugalizing for 1½ hours with 3000 revolutions a minute, all platelets may be precipitated, leaving a clear plasma which generally coagulates in from 8 to 14 minutes at 35° C. However, the clotting point is never so definite in this plasma, though the results may be quite interesting as a supplement to the examination of sedimentation plasma.

Any intermediary values found with plasma centrifugalized at low speed or only for a short time cannot be used. The difference between plasma centrifugalized and not centrifugalized is shown in Table 5.

Although the coagulation time is doubled in normal specimens, when the platelets are completely thrown down, this is not the case in pernicious anaemia with protracted coagulation time due to platelet insufficiency, as will be shown later.

In order to see whether the variations in coagulation time observed in recalcinated citrated plasma corresponded with variations in the coagulation time of venous blood, I have

carried out a series of observations of the coagulation time of venous blood.

The results were not very satisfactory, inasmuch as double specimens varied greatly, all determinations in normals however lying between 3 and 8 minutes (60 cases). Through a curved needle 1 c. cm. of blood was run down into a broad, flat-bottomed glass tube kept immersed in the Dewar flask.

TABLE 5

Name	Diagnosis	Sedimentation platelets c.t. min.	Centrifugal- ized platelets c.t. min.
O. J. ....	Nephritis .....	5½	13
L. K. ....	Cancer ventr. ....	4½	11
M. J. ....	Polyarthritis .....	5	12
G. A. ....	Normal .....	4	8½
H. N. ....	Normal .....	4½	12½
M. J. ....	Normal .....	4	11
G. K. ....	Normal .....	5	9
I. P. G. ....	Normal .....	4	11
J. J. ....	Normal .....	5	12
D. S. ....	Normal .....	4½	10½
N. J. ....	Dyst. musc. ....	5	14
J. N. ....	U. V. ....	5	9
X. X. ....	Hemorrh. corp. vitrei....	5½	13
K. H. ....	Fb. rheum. ....	3½	11
A. F. ....	An. pern. (remission)....	5½	9½
E. L. ....	An. pern. (remission)....	4	10½
K. J. ....	An. pern. (remission)....	6	14
M. J. ....	Fb. rheum. ....	6	10
A. K. ....	Influenza .....	6	10½
H. W. ....	Icterus chron. 1 yr.....	5½	12
J. O. ....	Vulnus oculi .....	5	9
E. P. ....	Pulm. tub. ....	5	9½
O. J. ....	Obstipation .....	4½	11½
Mean values .....		5	10½

The flask is turned to the horizontal position every thirtieth second till the blood stiffens. The narrow test-tubes used for the coagulation of plasma could not be used on account of the viscosity of the blood, which was apt to obscure the results.

The Lee & Vincent *Ca-in-vitro* test was carried out in many cases without ever showing definite evidences of lack of calcium even in cases of rather severe icterus of long duration. Table 6 shows a comparison between the results of determinations of the coagulation time of blood and plasma in some pathological cases, one case of haemophilia and four cases of pernicious anaemia. The platelet count by O. Thomsen's method is given on the extreme right.

TABLE 6

Name	Diagnosis	c.t. of plasma	c.t. of blood	Platelet count
		normal, 3-6 min.	normal, 3-8	normal, 200,000-350,000
P. H. ....	Hæmophilia .....	16	30½	402,000
A. P. ....	An. pernic. ....	8½	12	74,000
A. P. ....	An. pernic. ....	6½	9	83,000
J. N. ....	An. aplast. pern. ....	10	9	16,000
A. M. P. ....	An. pern. ....	11	10	7,000

The protracted coagulation time is evident both in blood and in plasma, the lengthening being most marked in the blood in haemophilia, in the plasma in pernicious anaemia. The

influence of temperature on the coagulation time of venous blood is the same as on plasma, as shown in Table 7.

TABLE 7

Name	Diagnosis	Blood	Blood
		c.t. minutes 35° C.	c.t. minutes 18° C.
A. L. ....	Diabetes .....	6½-7½	12½
J. J. ....	Ischias .....	6½-7	11½

If we tabulate the plasma clotting-time determinations carried out in normal persons and patients with "indifferent" diseases with normal platelet counts, we find the following:

TABLE 8

## NORMAL INDIVIDUALS

Coagulation time of plasma	Number of individuals	Number of determinations
3 minutes .....	4	4
3½ " .....	20	22
4 " .....	39	44
4½ " .....	32	38
5 " .....	38	45
5½ " .....	15	15
6 " .....	5	5
	109	173

In repeated determinations at weekly intervals in the same individual the variations are larger than in double specimens taken at the same time; the variations, however, are always within normal bounds.

Shortening of the coagulation time to 2 minutes has been observed in a few cases. No pathological significance can be attributed to these results, as, generally, they were not found on repeated examination. These variations may be due to bad venapuncture or unclean glasses. However, in convalescing pneumonias and anaemia due to malignant tumors, where the platelet count is high, rather low periods of coagulation time are often but not always met with. In a smaller number of normal individuals, the coagulation time varied between 3½ and 6 minutes.

The pathologically protracted coagulation times fall naturally into two groupings, those with and those without platelet deficiency.

A decidedly low platelet count, less than 200,000 per c. mm., is found in pernicious and aplastic anaemia, in certain infectious diseases, influenza-pneumonia, typhoid, etc., and in a few other conditions.

In a general way one may say that the coagulation time is prolonged beyond 6 minutes when the platelets fall below 200,000; the phenomenon however is constant only when the platelet count is less than 100,000 per c. mm.

There is, of course—as may be seen from the following tables—a relation between the fall of the platelet count and the protraction of the clotting-time, but this is not a mathematical relation which would enable us to calculate the other, when one of the factors is known.

The reason for this lies not in the experimental error which may of course play a rôle, but in the varying size of the platelets found in pathological conditions. The effect of this "anisothrombocytosis" is that the clotting power of a given

number of platelets varies in different cases, just as the oxygen capacity of a given number of red cells varies in micro- or megalocytosis.

If in dealing with the first group of cases we turn to the observations in pernicious and aplastic anaemia, we find the result of the first examination in 22 cases, 18 pernicious and 4 aplastic anaemias, in Table 9.

All cases were either fresh untreated cases or newly admitted relapses, excepting Cases 7 and 8, which were in different stages of a remission at the time of the first examination. In addition to the coagulation time and the platelet count the haemoglobin values are noted, to give an idea of the severity of the disease.

TABLE 9  
PERNICIOUS ANAEMIA

Name	Clotting-time, minutes	Platelets pr. c. mm.	Hb., per cent
1 E. L.	6	55,000	43
2 K. T.	8	58,000	36
3 A. F.	8	73,000	34
4 V. N.	7	140,000	76
5 A. M. P.	12½	13,000	13
6 C. S.	7	93,000	40
7 M. L.	7½	246,000	45
8 H. O.	6½	188,000	79
9 C. G.	5	116,000	52
10 M. T.	6½	193,000	56
11 A. P.	8	66,000	about 30
12 M. J.	4½	56,000	31
13 J. F.	9½	13,000	21
14 G. B.	6½	36,000	16
15 M. P.	11½	16,000	15
16 R. H. M.	11	21,000	25
17 I. W.	11½	22,000	28
18 E. O.	13½	4,000	21
19 J. N.	9½	20,000	28
20 W. K.	7½	105,000	aplastic
21 K. P.	9½	34,000	14
22 P. B.	7	72,000	38

The only cases showing a serious disagreement between platelet count and clotting-time are Nos. 7 and 12. Attention is drawn to the fact that the coagulation time of uncentrifuged plasma in pernicious anaemia never exceeds that of normal centrifuged plasma. In Table 10 the difference between uncentrifuged plasma is shown in a few cases of pernicious anaemia.

TABLE 10

Name	Clotting-time, minutes not centrifugized	Clotting-time minutes centrifugized	Platelet count per c. mm.
A. P.	8½	16	37,000
J. F.	9½	11½	13,000
J. N.	10	13½	11,000
J. N.	11½	13	5,000
V. N.	7½	12½	38,000
C. S.	7	10	93,000
E. O.	13½	16	4,000
A. P.	11	14½	6,000
E. L.	8½	10½	14,000
P. B.	7	8	72,000

It is apparent that the clotting time is only slightly prolonged by centrifugation in these cases, three of the cases

however slightly exceeding the normal limits for centrifuged plasma. This might point to an essential difference between the platelet deficit in pernicious anaemia and in purpura, where Hess has found normal plasma clotting-times which were not prolonged by centrifugation.

The variations in coagulation time during remissions and relapses in several cases follow the variations in the amount of platelets and are shown in Table 11.

TABLE 11  
REPEATED DETERMINATIONS IN PERNICIOUS ANAEMIA. THE NUMERALS FROM ABOVE IN EACH SQUARE SHOW DATE, PLATELET COUNT, CLOTTING-TIME AND HÆMOGLOBIN

	6-9	19-9	13-10	26-1-20	8-3-20			Remission and relapse.
K. T.	55,060	23,000	113,000	197,000	14,000	...	...	...
	6	9½	5	6	8½	...	...	...
	43	28	59	66	19	...	...	...
A. F.	29-12	5-1-20	26-1	8-3-20	...	...	...	Remission.
	58,000	38,000	75,000	194,000	...	...	...	...
	8	7½	6½	4½	...	...	...	...
	36	31	49	76	...	...	...	...
V. N.	3-12	22-12	5-1	8-3-20	...	...	...	Remission.
	73,000	58,000	344,000	362,000	...	...	...	...
	34	25	43	70	...	...	...	...
J. N.	15-2	15-3	5-1	19-1	8-3	...	...	First two examinations during remission, then relapse and new remission.
	140,000	181,000	77,000	45,000	106,000	...	...	...
	7	6	6	7½	6½	...	...	...
	76	?	45	47	65	...	...	...
W. K.	22-12	24-12	5-1	1-2	...	...	...	Died.
	20,000	11,000	5,000	16,000	...	...	...	...
	9½	10	11½	10	...	...	...	...
	25	24	26	12	...	...	...	...
C. G.	20-2	25-2	...	...	...	...	...	Died.
	105,000	40,000	...	...	...	...	...	...
	7½	11½	...	...	...	...	...	...
	47	35	...	...	...	...	...	...
A. P.	31-5	7-6	14-6	21-6	25-6	7-7	...	Remission.
	116,000	108,000	90,000	173,000	177,000	263,000	...	...
	6	6½	7½	5	6	6	...	...
	52	50	58	63	73	82	...	...
A. P.	6-3	11-3	21-3	1-4	24-4	14-5	14-6	Slight remission, then relapse and death.
	66,000	61,000	74,000	55,000	83,000	95,000	74,000	37,000
	8	7½	8½	6½	6½	7	7	8½
	about 30	?	?	?	46	47	49	32
I. W.	27-10	7-11	28-11	5-19	...	...	...	Died.
	22,000	41,000	42,000	26,000	...	...	...	...
	11½	9	6½	7	...	...	...	...
	28	30	36	31	...	...	...	...
A. P.	25-2	26	...	...	...	...	...	Died.
	13,000	7,000	...	...	...	...	...	...
	12½	11	...	...	...	...	...	...
	13	13	...	...	...	...	...	...

In three cases of myeloid leukaemia with normal or increased platelet count the coagulation time was normal.

In two such cases with periods of low platelet count and symptoms of a haemorrhagic diathesis, the clotting-time was protracted, when the count was at its lowest.

TABLE 12  
MYELOID LEUKAEMIA WITH PLATELET DEFICIT. THE NUMBERS FROM ABOVE IN THE HORIZONTAL COLUMNS GIVE DATE, PLATELET COUNT, CLOTTING-TIME, HÆMOGLOBIN AND LEUCOCYTES

M. J.	24-2	5-3	12-3	Slight improvement. Discharged for private reasons.
	75,000	115,000	134,000	...
	6½	5	5½	...
	47	...	...	...
	240,000	...	...	...
E. E.	24-9	16-12	...	Increasing anaemia. Died.
	405,000	90,000	...	...
	5½	3½	...	...
	7	33	...	...
	22,500	18,200	...	...

In one case of lymphatic leukaemia with normal platelet count the clotting-time was normal.

In three other cases with low platelet counts, the clotting-time was protracted in the two that showed the lowest number.

TABLE 13  
LYMPHATIC LEUKÆMIA WITH PLATELET DEFICIT

	29-3	7-4	22-4	21-6
J. B.	170,000	175,000	156,000	130,000
?	5	5	5	44
?	2	2	68	66
?	2	2	247,000	63,100
C. M.	26-5	....	....	....
49,000	....	....	....	....
61	....	....	....	....
51	....	....	....	....
3,200	....	....	....	....
A. S.	21-2	....	....	....
131,000	....	....	....	....
7	....	....	....	....
85	....	....	....	....
120,000	....	....	....	....

On the whole a platelet deficit in leukæmia seems not to protract the coagulation time as much as does a similar change in pernicious anaemia.

In a few other cases a low platelet count and possibly a functional insufficiency of the amount present may also have played a part in prolonging the clotting-time.

TABLE 14  
PROTRACTED CLOTTING WITH DECREASED OR LOW NORMAL PLATELET COUNTS IN VARIOUS DISEASES

Name	Diagnosis	Date	Platelets	Clotting-time	Died.
E. M.	Pneumonia.	Date .....	10-5	....	....
		Platelets .....	247,000	....	....
		Clotting-time .....	6½	....	....
C. C.	Purpura. Anæmia. Endocarditis.	Date .....	112,000	....	....
		Platelets .....	....	....	....
		Clotting-time .....	7	....	....
O. P.	Acromegaly. Anæmia.	Date .....	7-2	....	....
		Platelets .....	233,000	248,000	200,000
		Clotting-time .....	S	6	S½
I. O.	Tumor lienis. Anæmia.	Date .....	7-3	....	....
		Platelets .....	205,000	....	....
		Clotting-time .....	7½	....	....
M. K.	Influenza.	Date .....	12-1	22-1	....
		Platelets .....	157,000	247,000	....
		Clotting-time .....	S½	6	....

In several other cases of influenza and influenza-pneumonia examined the coagulation count was normal; the platelet count, however, never went below 100,000 per c. mm.

The other group is represented only by three cases of haemophilia, all three with a typical family history.

TABLE 15  
HÆMOPHILIA

Name	Date	Platelets	Coagulation time	
P. H.	Date .....	23-4	27-5	Pronounced case with hemorrhage and joint affections.
	Platelets .....	402,000	457,000	
	Coagulation time .....	16	14½	
I. C.	Date .....	27-5	....	Pronounced case with hemorrhage and joint affections.
	Platelets .....	394,000	....	
	Coagulation time .....	13	....	
S.	Date .....	26-6	....	Light case in an elderly man.
	Platelets .....	528,000	....	
	Coagulation time .....	7½	....	

Unfortunately I have not determined the coagulation time of centrifuged plasma in these cases, the excess of plasma being used for other purposes. \*

However, I observed that a larger amount of plasma than was recalcinated with the optimal amount of Cacl<sub>2</sub> solution took some 50 minutes to clot firmly, the end point being very difficult to fix, since the coagulation proceeded very slowly.

It seems that by centrifugalizing one accentuates the difference between normal and haemophilic blood, whereas in pernicious anaemia quite the opposite is observed.

Attention is drawn to the fact that the coagulation time in the first case of haemophilia is longer than that of normal platelet-free plasma.

#### SUMMARY

1. A method is described by which the clotting-time of citrated plasma may be determined at 35° C. in tubes placed in an unsilvered Dewar flask. The procedure is a modification of Howell's principle of optimal recalcination, and may be performed on the same blood specimen as that employed for the Oluf Thomsen method of counting the platelets.

2. In normal individuals the clotting-time of the optimally recalcinated tube lies between 3-6 minutes for uncentrifuged plasma, and generally between 8-14 minutes for platelet-free plasma, that has been centrifugalized for 90 minutes at high speed.

3. The reasons for choosing the first are the following:

(a) No centrifuge is needed.

(b) The change from the liquid to the solid state is sharper.

(c) The result shows changes both in the platelet count and in the clotting power of the plasma proper.

4. The necessity for maintaining a constant temperature (best 35° C.) in coagulation experiments is shown.

5. It is shown that the variations in clotting-time of optimally recalcinated plasma correspond with those of venous blood.

6. It is shown that the coagulation time of uncentrifuged plasma is longer than normal in the haemorrhagic diathesis with platelet deficit—pernicious anaemia, leukæmia and various other diseases.

7. In haemophilia the coagulation time is very much longer than normal, although a perfectly normal number of platelets is present.

8. The method is of importance for the diagnosis of haemophilia if combined with a determination of the platelet count after Oluf Thomsen's method. It may also reveal the existence of a haemorrhagic diathesis in the course of diseases of the blood. If haemophilia can be excluded, a prolonged coagulation time means that there is a numeral, or partially functional, deficiency of platelets, though the converse need not be true.

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# THE ORIGIN OF HÆMANGIECTASES

By T. S. MOISE

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## INTRODUCTION

The origin and nature of angioma of the liver have been the subject of prolonged discussion by many authors. Two general ideas have been proposed: one, that angioma are new growths; the other, that they are merely capillary dilatations resulting from various causes. Among the advocates of the new-growth theory some believe that they are primarily connective-tissue tumors and others that they are vascular in origin. Virchow<sup>1,2</sup> advanced the former idea, proposing that the process begins with a proliferation of connective tissue and that finally the newly formed capillaries dilate to form a cavernous ectasia. This theory has been advocated from time to time by different observers (Rindfleisch,<sup>3</sup> Burekhard<sup>4</sup>), although an explanation of the cause for the capillary dilatation is lacking. Ribbert<sup>5</sup> proposed the theory that hemangioma are new growths arising from the proliferation of misplaced vascular rests, which in turn result from developmental abnormalities. MacCurdy<sup>6</sup> has recently suggested that angioma and many endothelioma arise from anlagen of undifferentiated cells having the triple capacity of forming blood cells, blood vessels and lawless tumor cells.

In contrast, Borst<sup>7</sup> concluded that most angioma are not new growths, but result from a metamorphosis of blood vessels with capillary ectasia and secondary connective-tissue proliferation, and that only rarely are they vascular neoplasms. Schmieden<sup>8</sup> was of the opinion that the liver cavernoma are developmental anomalies, and that their final form is determined by secondary regressive changes in the liver cells. Hæmorrhage, chronic passive congestion, a "hyperæmia ex vacuo" secondary to atrophy of the liver cells, capillary dilatation and even congestion of bile, as well as many other theories, have been advanced to explain the origin of these structures (Sheffen,<sup>9</sup> Benecke,<sup>10</sup> et al.).

This paper is based on the study of diffuse hæmangiectases involving particularly the liver, kidneys, and adrenal glands. The condition is interesting on account of its rarity. Furthermore, its study has suggested a mechanistic origin for angioma. The theory is based upon fundamental principles of the development and growth of the vascular system and on certain observations which, although previously made, are a conspicuous feature of this case.

## CASE REPORT

The case was one of general carcinomatosis from a primary tumor of Bartholin's gland. The clinical history pertains entirely to this condition. The abstract of the protocol

\* The author wishes to express his appreciation to Dr. J. T. MacCurdy for the use of his unpublished manuscript, "The Relation of Autochthonous Blood Cells and Endothelial Proliferation to Angioma and Endothelioma."

presented below will include only those features which have a direct bearing on the angioma.

**AUTOPSY No. 201.—Liver.**—The liver weighs 3700 grams and measures 37 by 28 by 10 cm. Grossly, it shows a mottling of alternate dark red and lighter colored areas. On section the periportal areas are definitely outlined by dark red lines, and the lobules are distinctly seen.

Microscopically, the liver shows numerous blood channels situated chiefly in the periportal region, forming a chain of dilated sinuses surrounding the lobules (Fig. 1). In many areas this process extends beyond the confines of the peripheral zone, and the lobular architecture is wholly or partly obliterated by groups of dilated blood spaces that are typically cavernous in type. These sinuses are filled with blood, but the effects of pressure on the surrounding parenchyma are not conspicuous. In other areas small dilated capillaries extend into the middle and central zones of the lobules, and in still other areas the picture of chronic passive congestion is seen. The blood channels are irregular in size and shape, intercommunicate freely, and are completely or partially separated from one another by septa of normal liver cells or bands of connective tissue. They are lined with a single layer of conspicuous endothelial cells. Actual formation of new capillaries is not seen in spite of a careful study by serial sections.

Perhaps the most interesting feature of the liver angioma is the evidence of hæmatopoiesis. The blood channels contain many immature cells of both the erythroblastic and myeloblastic series (Fig. 2).

**Kidneys.**—The two kidneys are similar. They are not enlarged, and externally, as well as on section, their appearance is normal except for congestion.

Microscopically, there is a less extensive, but only a slightly less conspicuous, hæmangiectatic process than was described for the liver. There is a diffuse involvement of the vessels of the glomeruli, labyrinth, and pyramids. All gradations are encountered, from slight dilatation of the vessels of a glomerulus to a practically complete involvement and conversion of the structure into a dilated vascular channel (Fig. 3). The other vessels show a dilatation of the telangiectatic rather than of the cavernous type. Although not a conspicuous feature, a few of the dilated blood spaces in the glomeruli show nucleated red blood cells as evidence of blood formation.

**Adrenals.**—The adrenals show a diffuse telangiectasis. The process involves the cortex extensively and the medulla to a lesser degree. There is definite evidence of blood formation in the presence of nucleated red blood cells and young cells of the myeloid series.

The heart muscle, the spleen, and pancreas also contain dilated vessels, but the process is not sufficiently definite to allow the conclusion that the same changes are present in these organs as were found in the liver, kidneys and adrenal glands.

In summary, there is extensive diffuse hæmangiectasis of the liver situated in the periportal region, an unusual type of bilateral diffuse hæmangiectasis of the kidneys involving all portions of the medulla and cortex, but most markedly the glomerular tufts, and a similar diffuse process in the adrenal glands. Furthermore, in all three organs evidence of hæmatopoiesis is easily recognizable.

## DISCUSSION

The usual cavernomata of the liver are without clinical symptoms and are of theoretical interest only. They are relatively common at the autopsy table and their etiology has been widely discussed. They are frequently multiple, usually small, and sometimes are associated with angioma of other organs. They may be on the surface or buried deep within the liver substance as sharply outlined, deep purplish-red areas. Microscopically, there is a variable amount of connective-tissue proliferation which sharply outlines the angioma. They consist of numerous freely anastomosing, dilated, vascular channels, separated by thin septa of fibrous tissue or of liver cells.

The discussion of the relation of the blood channels of cavernoma to the normal vessels of the liver shows great difference of opinion. Many observers have made injections through the portal and hepatic veins, the hepatic artery and the cavernoma itself. Some have succeeded and others have failed to demonstrate a connection between the cavernoma and the general circulation. The majority of authors have not found a free connection, although confirmation of either view is easily found. In the face of such variable results, it is probable that the connection is not free in many cases.

There is also a great difference of opinion concerning the presence of a true growth of capillaries. MacCurdy<sup>6</sup> studied a series of thirty hæmangioma involving the liver, spleen, intestine, skin, heart valves, kidneys, nasal mucosa, and the popliteal space, and states that: (1) all the cavernomata contain areas showing the simpler capillary type, (2) if numerous sections are made, growing capillaries are always found, some of which have endothelium proliferating to form several layers, (3) there are always areas showing proliferation of endothelium into the surrounding connective tissue and parenchyma, (4) evidence of blood formation is seen in all cases. The majority of cases on record do not confirm MacCurdy's view that true vascular growth is universally present.

On the other hand, his conclusion concerning the persistence of hematopoiesis has been confirmed by the author in recent studies of angioma of the liver, skin, and testicle.\* This observation has been made before. For example, Pilliet<sup>11</sup> describes six hæmangioma and Schmieden<sup>8</sup> two showing evidence of blood formation. In addition to similar findings, in every case of his series, MacCurdy believes that he has found evidence of hematopoiesis in the literature, in the drawings and descriptions of other authors who have not appreciated the significance of the cells they described.

Circumscribed liver cavernomata are quite common in the literature, but a diffuse process such as is reported in this paper is relatively uncommon. Major and Black<sup>12</sup> report a case in which the liver weighed 18,160 grams and measured 35 by 44 by 11 cm. The liver tissue was largely replaced by

a spongy network filled with clotted blood. The microscopic picture was that of large dilated blood channels. There was extensive destruction of the liver, and in some places an overgrowth of fibrous tissue with evidence of active connective tissue and capillary proliferation. The relation to the portal or hepatic veins was not discussed. In addition there was an hæmangioma of the skull and bilateral cystic adrenals. Mantle<sup>13</sup> describes a case in which the tumor measured 30 by 16 by 4 cm. Grossly, the right lobe was involved in a large cavernous angioma, while the left lobe was unaltered. Microscopically, the main mass of the growth showed irregular vascular channels separated by septa of dense fibrous tissue. The blood spaces were very large and were crossed by trabeculae of fibrous tissue containing bile-ducts and occasional collections of hepatic cells. At the margin of the growth there was no capsule separating the tumor from the adjacent liver tissue and the vascular channels were dilated in the periportal zones of the neighboring lobules. In the left lobe there was also some dilatation of the branches of the portal canals but the liver substance was normal. Mantle<sup>13</sup> says, "This growth had apparently originated in the dilatation of pre-existing vessels rather than in a new formation. This is shown by the presence of hepatic cells and bile-ducts throughout the growth and by dilatation of the vessels of the left lobe." Schrohe<sup>14</sup> adds an example of an hæmangioma of the liver identical with the one contributed in this communication, except that evidence of hematopoiesis is not mentioned. Langer<sup>15</sup> extirpated a large angioma of the liver weighing 5000 grams and measuring 21 by 21 by 11 cm. The main mass was a typical cavernoma, but he describes a dilatation of the vessels in the normal liver substance at the periphery of the tumor, and, according to his illustrations, the dilatation was limited to the periportal area.

Borst<sup>1</sup> describes a case showing dilatation and enlargement around the central veins and says that interesting changes were encountered in different portions of the liver. These showed stretching of the vessels, then a telangiectasis, and finally, a cavernous metamorphosis. Roggenbau<sup>16</sup> reports a large hæmangioma involving the whole left lobe, the left half of the right lobe, and the quadrate lobe. The liver in this case measured 22 by 33 by 9 cm. The main mass showed typical irregular cavernous spaces. At the periphery of the various tumor masses, where the involvement was less marked, the central veins and their branches were dilated. Furthermore, there was a simultaneous proliferation of new vessels and connective tissue. M'Weney<sup>17</sup> describes a case in which the liver weighed 5100 grams (180 oz.) and was transformed into a large angioma measuring 25 by 25 by 10 cm. There were also dilatation and widening of the branches of the central veins. Wagner<sup>18</sup> describes a similar case and MacCurdy<sup>6</sup> mentions one showing dilatation of the vessels in the central zones, but he does not consider this case analogous to the usual cavernoma.

There are also cases recorded of large angioma of the liver removed at operation in which the condition of the remainder of the liver could not be determined.

The small number of cases of diffuse involvement of the liver fall into certain groups: one, in which there is a close relation

\* This opinion was also confirmed in an hæmangioma of the skin of a new-born infant. The blood in the general circulation showed no evidence of hematopoiesis, but nucleated red blood cells were easily found in blood smears from the angioma.

to the portal vein and its branches; another, in which a similar relation to the central veins is described, and, as might be expected, some in which the extent of the process is greater and no such relation is apparent.

The usual cavernoma is circumscribed. It may be single or multiple and involve either the liver only or several organs. Diffuse haemangiectases are rare and the association of such a diffuse process in the liver, kidneys, and adrenals as is found in the case reported here has not been previously described.

#### THE ORIGIN OF HAEMANGIECTASES

Before proposing an explanation for the origin of haemangiomas, a review of some general principles of the development and growth of the vascular system is essential.

The first tissue of the embryo that exhibits unquestionable differentiation (Minot<sup>19</sup>) is the angioblast or primitive vascular anlage. The angioblast appears on the yolk-sac as a group of blood vessels forming the vitelline capillary plexus and covers the entire yolk-sac in the earliest human embryos. There have been two opinions held as to the further development: one, that there are other vascular anlagen derived from the mesoderm directly, and, accordingly, that there are many sources of early blood vessels; the other, that the entire vascular system is derived from growth and extension of the vitelline capillary plexus (Evans<sup>20</sup>).

For a long time it has been possible to show that all vessels formed subsequent to the development of the aorta arise as capillary sprouts from pre-formed endothelium. Bremer<sup>21</sup> has demonstrated in the head of a rabbit embryo of five somites that the aorta is represented by a capillary plexus coterminous with the vitelline capillary plexus. This fact probably indicates that the entire vascular system arises from a budding of the primary angioblast of the yolk-sac. The Swiss anatomist, Aeby,<sup>22</sup> expressed the opinion in 1868 that the vascular system originally existed as a uniform capillary meshwork of vessels. This idea has been strongly opposed until recently, when it has been shown by the injection of living embryos that the early vascular system does appear in a multiple capillary form. Evans<sup>20</sup> states that this represents the fundamental method of vascular growth, and that the larger vessels come into existence only by the enlargement of certain fortuitously situated capillaries which assume a larger and larger function and develop into arteries at the expense of other capillaries which accordingly must regress. Growth, however, is not a function confined to the capillary plexus alone, as branches may also arise from embryonic arteries after they are differentiated as such. The most familiar example of the operation of this principle is seen in the growth of granulation tissue which, in its beginning, is a highly vascular tissue consisting of numerous capillary loops, while the end result, scar tissue, is relatively avascular.

In some organs, the liver for example, the blood vessels arise in a different way (Mall<sup>23</sup>). Here, the method is invasion of large venous trunks, the omphalomesenteric veins, by the glandular tissue in such a way that the main trunk becomes broken into a large number of smaller vessels. The

vessels formed in this way (the so-called sinusoids) are markedly irregular and are often much larger than the usual capillaries.

In his study of the structural unit of the liver, Mall<sup>23</sup> has discussed the histomechanical principles of Thoma<sup>24</sup> in relation to the vascular growth in that organ. Thoma's three laws are as follows:

"The increase in the size of the lumen of the vessel, or, what is the same thing, the increase in the surface of the vessel wall, depends on the rate of the blood-current. The surface of a vessel wall ceases to grow when the blood-current acquires a definite rate. The vessel increases in size when this rate is exceeded, becomes smaller when the blood-stream is slowed, and disappears when it is finally arrested.

"This law which brings the growth of the surface of the vessel wall into dependence upon the rate of the flow of blood is, I consider, the first and most important histo-mechanical principle which determines the state of the lumen of the vessel under physiological and pathological conditions.

"A second histo-mechanical principle may be added to this, viz., the growth in thickness of the vessel wall is dependent upon its tension. Further, the tension of the wall is dependent upon the diameter of the lumen of the vessel and upon the blood pressure.

"The third histo-mechanical principle has not hitherto been so completely demonstrated as the first two. It will, therefore, be put forward merely as an hypothesis, which runs as follows: increase of blood pressure in capillary areas leads to new formation of capillaries."

In his study of the liver, Mall has shown that the first two principles of Thoma are applicable, but in reference to the third principle that factors other than blood pressure are of importance in the formation of new capillaries, we may quote Thoma<sup>24</sup> further:

"According to the generally accepted view of the problem of circulation, which was formerly quite sufficient to serve as a basis for the account of its general disturbances, the pressure, the rate, and the amount of blood-flow appeared to be directly dependent upon the action of the heart. According to the view given here, on the other hand, it is the metabolic processes in the organs, which determine first for the individual organs, then for the whole of the organs—that is, for the circulation as a whole—the amount of blood propelled within a given time, its pressure, and its rate of flow. In this case the working-power of the heart appears as the equivalent of the sum of the histo-mechanical demands made by the organs."

Mall<sup>23</sup> and Thoma<sup>24</sup> find that the capillaries of like component parts of an organ are of equal size and length, and that the rapidity of the circulation through them is equal. This is brought about by the action of mechanical laws; with a greater flow of blood, a capillary dilates and becomes converted into an artery or vein, other channels in which the rate of flow is constant remain as capillaries, and, lastly, some channels offering great resistance are slowly traversed and gradually disappear.

In his study of the liver, Mall<sup>23</sup> points out that the capillaries of the liver lobule consist of long capillaries and short capillaries. By an elaborate model of the lobule, he demonstrated that the long and short capillaries are equally favored by the circulating fluid. This was apparently a stumbling block. Further study showed, however, that the

long capillaries of contiguous lobules converge toward that portion of the interlobular fissure in which there are no collecting veins. This immediately suggested that some of the main capillaries would be converted into veins, which is the case in growing livers, but with each new vein a new vascular unit is formed and two new nodal points complicate the picture (Mall<sup>2</sup>).

From this very brief consideration of the embryology of the circulatory system in general, of Thoma's laws, and of their application to the liver, it is evident that: (1) the general mode of development of the vascular system is in the form of a primary capillary plexus; (2) certain capillaries undergo regression, others remain stationary, and others develop into larger vessels forming the arteries and veins to the part; (3) the growing capillary system in obedience to the laws of mechanics is a changing and variable structure.

On this basis, many vascular abnormalities are easily explained. A persistence of certain parts of the original capillary plexiform anlage may explain the origin of the hæmangioma or hæmangiectases of various organs. The complicated, ever-changing vascular system of the liver is likely to be a favorite site for such changes. The explanation of why these capillaries persist may offer some difficulty. It is obvious that these vessels, normally undergoing regressive changes on account of the lack of sufficient hydrodynamic force to maintain their circulation, will not remain patent unless the circulation through them is maintained. In this connection the retention of the function of hæmatopoiesis is significant. The continual formation of blood cells, if present, may supply the *vis a tergo* necessary to keep these vessels open. The same factors at work in the normal obliteration of these vessels may be active and offer some hindrance to the egress of blood elements formed *in situ*, and in this way tend to maintain a higher pressure with resulting distention. The well-known fact of the great increase in resistance produced by the insertion of angles or elbows in an hydraulic system is applicable, and the difficulties these angles may offer in the way of satisfactory injection experiments is obvious.

In the absence of hæmatopoiesis, resistance to the outflow (*e. g.*, by angles) or forces similar to those in operation at the nodal points of the liver may be present, and it seems possible that a study of the architecture of angioma by means of corrosion specimens with injection of the general circulation and of the angioma, as well as a similar study by various reconstruction methods, may demonstrate the presence of sufficient mechanical factors to explain the occurrence of these structures.

It seems probable that angioma may be explicable on this basis, and that the cases showing real growth of blood vessels may be the result of a secondary change in the walls of a simple hæmangiectatic structure.

#### SUMMARY

1. Diffuse hæmangiectases of the liver are rare and the association with a similar process in the kidneys and adrenal

glands as reported in this paper has not been previously described.

2. Hæmatopoiesis is not infrequently observed and may be present in all angioma. Further confirmation of this point is desirable.

3. The early vascular system develops in the form of a capillary plexus. The subsequent growth of certain capillaries and the regression of others are controlled by the laws of mechanics.

4. The persistence of capillaries which normally undergo regressive changes offers an explanation for the occurrence of hæmangioma or hæmangiectases.

To prove this theory it is necessary to determine what forces are present to maintain the patency of these vessels. Hæmatopoiesis may supply the necessary force. Furthermore, other mechanical factors may be important. In order to clarify this point, it is desirable to determine whether blood formation is present in all hæmangioma and to study these structures by injection and by reconstruction methods.

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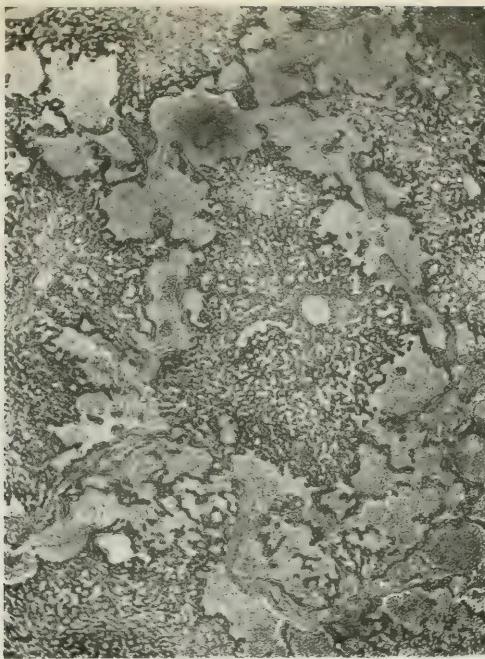


FIG. 1.—Diffuse haemangiectasis of the liver. A section showing the periportal distribution of the dilated sinuses. ( $\times 55.$ )

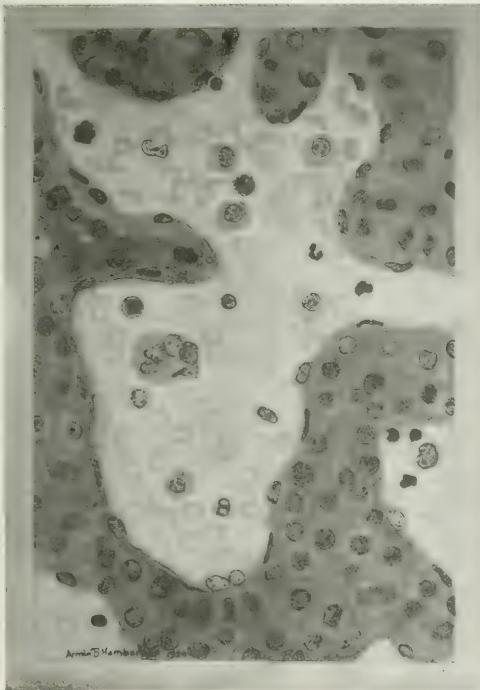


FIG. 2.—Diffuse haemangiectasis of the liver. A high-power drawing of a dilated sinus, showing nucleated red blood cells and immature cells of the myeloid series as evidence of hematopoiesis. ( $\times 800.$ )

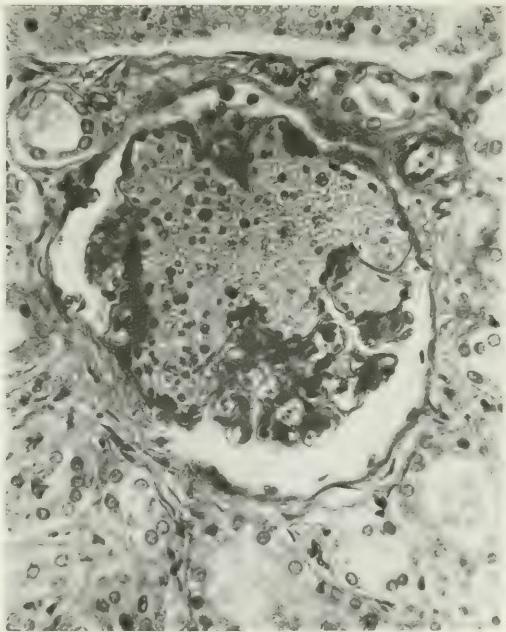
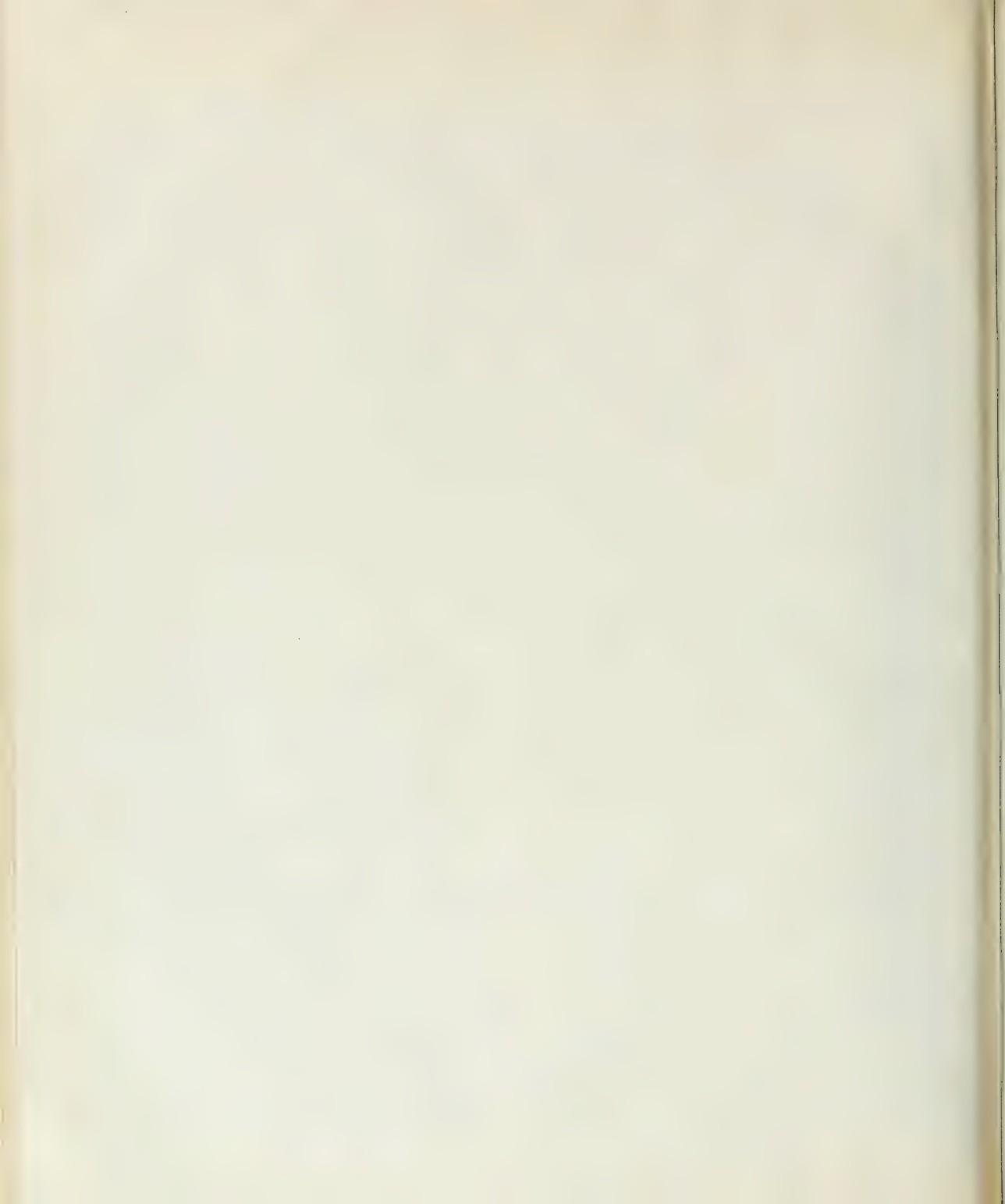


FIG. 3.—Diffuse haemangiectasis of the kidneys. A section showing extreme dilatation of the vessels of a glomerular tuft. ( $\times 375.$ )



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## CHEMICAL STRUCTURE AND PHYSIOLOGICAL ACTION\*

By H. H. DALE

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In my previous lecture I asked your attention to the available evidence as to the intimate mechanism of the anaphylactic shock. There are many broader considerations of the meaning of the anaphylactic condition which are worthy of attention, but I can touch upon a few only. From the teleological point of view, the phenomena present at first sight some difficulty. Of what value can it be to the individual, or to the species, that one injection of a harmless substance should be followed by such a change in the constituents of the cells or the body fluids that the same substance, if again injected, acts as an acute, often as a lethal, poison?

The meaning begins to be clearer when we recognize that anaphylaxis is not, as its name was intended to imply, the opposite or antithesis of immunity, but a phase in the development of immunity, in which the immune substance or antibody has a peculiar distribution. We must recognize, further, that the danger to the individual of the anaphylactic state is largely the effect of the purely artificial conditions which we impose by the use of the hypodermic needle, by means of which we bring a foreign protein into the circulation with a rapidity which no natural method of absorption could achieve. Fundamentally the immune reaction, of which anaphylaxis is a specialized phase, represents the need of the species to prevent the permanent incorporation into the cells of protein having a different type from its own. That such incorporation, at least into the surface of the cell, may temporarily occur, is demonstrated by certain of the phenomena of anaphylaxis itself. We have seen how the precipitin from the serum of an immunized rabbit can be taken up by the cells of a guinea-pig, which is thereby rendered passively anaphylactic to the substance against which the rabbit had been immunized. Weil demonstrated that the passive anaphylaxis thus conferred lasted only for eight or ten days, at the end of which time its disappearance coincided with the appearance of a new, active anaphylaxis to rabbit protein. The guinea-pig, in thus becoming anaphylactic, has rid its cells of the rabbit protein, which they had for the time incorporated, and prepared them

to deal more rapidly with any new intrusion of the same protein. If the next invasion is sufficiently sudden and massive, the shock of the resisting mechanism, dangerously located to meet such attack in the vital cells of the organism, may lead to the death of the individual. With successful resistance to a series of milder and more gradually developed attacks, such as the organism is likely to meet under natural conditions, as contrasted with those created by the injection needle, the defensive mechanism is strengthened and extended beyond the cells, and the immune body circulates in sufficient excess in the blood to meet the invading foreign protein and secure its harmless removal from the sphere of action. A true immunity has been established.

In the anaphylactic shock we may contemplate the sacrifice of the individual to the purity of the type. Note that it is the proteins in particular from other species, against which this defensive system of anaphylaxis and immunity is prepared. It is the proteins which give to the species its distinctive biochemical character. The same fats and carbohydrates are found in a multitude of different types; the composition of an animal's body fat may change to some extent with the fats supplied in the food. According to recent evidence, it would appear that the lipoids and even the nucleic acids have the same composition through a wide range of species. The carbohydrates and fats are fuel supplying energy; the lipoids and nucleic acids seem to have the function of conferring on the cell protoplasm the physical characters on which its vital activities depend and of furnishing the supporting framework of the structures with which the physiological functions of the cell are inseparably connected. But, as Loeb and Levene have recently pointed out, it is on a difference of the proteins that the difference between species depends. One cannot imagine any replacement of the proteins of one species with those from another without loss of the specific character.

Against such intrusion the unicellular organism can apparently guard itself by the aid of its proteolytic ferment. In the higher animals this power of digesting foreign proteins is wanting, or held in abeyance, in the ordinary cells of the body, and the function is concentrated in the cells of the digestive glands. Ordinarily the digestive juices afford efficient protection to the body against the introduction of proteins foreign to its constitution, splitting the proteins of the food into their constituent amino-acids, from which, in

\* Lecture III of the Herter Series, delivered before The Johns Hopkins University on Nov. 15, 1919.

† It should be noted that in the lectures published in the August and September numbers, Dr. Dale was down as representing the Lister Institute of Preventive Medicine, which was incorrect.

due course, proteins with the architecture characteristic of the species can be built up. Occasionally the protection fails, as in the cases of alimentary anaphylaxis. As a rule, however, it is only when the foreign protein is introduced by some other route than that of the alimentary canal, that it passes uncloven into the blood stream and calls into action the secondary provision for its ultimate elimination. Nor is it only the proteins from *foreign* species which meet with this opposition to their permanent incorporation into the body cells in general. In some cases proteins from certain organs of the animal's own body, being presumably of a specialized type, are treated as foreign to the rest of the body, if they abnormally pass into the general circulation, and evoke a response of the mechanism of anaphylaxis and immunity.

It would lead me far beyond the limits of my time, and of my competence, to attempt to deal with the relation between anaphylaxis, seen in its simplest form in experiments with pure proteins, and the physiological changes accompanying the body's resistance to foreign protein introduced more gradually into the tissues of the circulation by the growth of microorganisms. That there is a very suggestive connection between some of the phenomena constituting the clinical disease produced by infection, and those of the anaphylactic reaction as seen in experiment, is, I think, abundantly clear, and it has received emphasis in the writings especially of Vaughan, Friedberger, and more recently Noy.

I must be content, moreover, with a mere reference to the much clearer connection between experimental anaphylaxis and certain natural or acquired idiosyncrasies to foreign protein, whether taken in the food, as in the fairly numerous well marked cases of intolerance for egg-protein which are on record, or absorbed through the respiratory mucous membrane, as in the cases of intolerance for the exhalations of certain animals, or the pollen of certain plants.

I want to ask your attention rather to what is at present the more academic problem of the nature of the difference which makes the protein of one species *foreign* to, that is to say, unsuitable for incorporation into the tissues of another. What is the nature of the difference which the anaphylactic or precipitin reaction detects in proteins which, to ordinary methods of appreciation, are so strikingly similar?

I may remind you that the protein molecule is built up from a number of different amino-acids, linked together into peptide chains, which chains, being again linked into an intricate skein, build up a molecule of immense complexity. We may distinguish three kinds of difference, which the reaction of immunity or anaphylaxis can detect.

1. There are cases in which a difference of antigenic properties can be related to a difference of chemical constitution so crude that a mere hydrolysis of the two proteins into their constituent amino-acids suffices for its detection. The different amino-acids are found to be present in widely different proportions in the two proteins; certain amino-acids may be present in the one which are not represented at all in the constitution of the other. The two proteins are obviously different chemical substances, and the difference is revealed

by a relatively superficial analysis. While it may be said, on the one hand, that no difficulty of conception is presented by the fact of their different antigenic properties, it does not, on the other hand, give us any clue to the nature of the relation between antigen and antibody which thus discriminates between them. As an instance of antigenic disparity between proteins having such obvious difference of constitution, we may take the case of the albumin and globulin from the same serum.

When analyzed into their amino-acids these at once show a pronounced difference of structure; the albumin, for example, contains much more lysine than the globulin, while glycine, which is well represented in the globulin molecule, appears to be absent altogether from that of the albumin. Hartley and I found that the pure albumin and euglobulin, which he had prepared from horse-serum, acted as completely distinct antigens. Not only did the guinea-pig sensitized to euglobulin

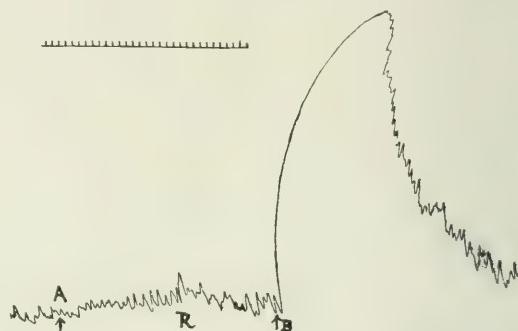


FIG. 1.—Guinea-pig sensitized with 1 mgm. of euglobulin. 17th day. A, 5 mgm. of albumin. B, 1 mgm. of euglobulin. (Dale and Hartley, Biochemical Journal, Vol. X, p. 421, Fig. 5.)

fail to react to albumin, and *vice versa*; in the guinea-pig rendered sensitive with whole horse-serum anaphylaxis to euglobulin appeared and attained its maximum, much earlier than that to albumin. (See Fig. 1. The tracing records contraction of the isolated uterine plain muscle.)

2. The two globulins of a serum—the so-called euglobulin and pseudoglobulin—present a difference of another kind. They are built up of the same amino-acids in apparently identical proportions, and even the finer method of structural investigation, presently to be discussed, fails to detect any difference between them. They show, however, a pronounced difference in their physical properties and solubilities, the euglobulin being quite insoluble in pure water and needing the presence of acid, alkali and a neutral salt to disperse its aggregates and bring it into colloidal solution, while the pseudoglobulin is taken up by pure water like an albumin. This difference between the globulins appears to be due to the fact that, in the euglobulin, a phosphorus-containing lipoïd is associated with the protein. The physical difference thus conferred is again associated with an antigenic disparity. Hartley and I found that a guinea-pig rendered sensitive

to the euglobulin of horse-serum was not sensitive to the pseudoglobulin (Fig. 2). The fact that guinea-pigs sensitized to the pseudoglobulin showed a minor degree of sensitiveness to the euglobulin also, is probably to be attributed to the extreme difficulty of purifying the pseudoglobulin completely from residual traces of euglobulin.

3. The most interesting cases, however, and till quite recently the most mysterious, are those in which neither an ordinary analysis into amino-acids, nor an examination of the physical properties, reveals any difference between two proteins, which are shown by the immunity reactions to be

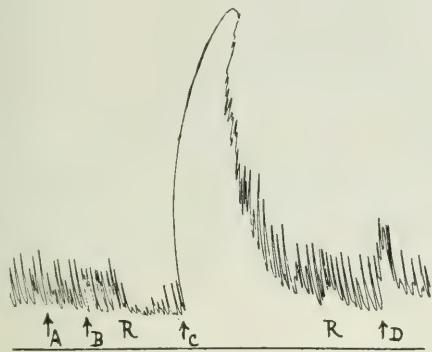


FIG. 2.—Guinea-pig sensitized with 1 mgm. of euglobulin. 13th day. *A*, 1 mgm. of pseudoglobulin. *B*, 10 mgm. of pseudoglobulin. *C*, 10 mgm. of euglobulin. *D*, 10 mgm. of euglobulin. (Dale and Hartley, Biochemical Journal, Vol. X, p. 422, Fig. 6.)

different substances. Abundant examples can be found in corresponding proteins from species not too widely separated—caseins from cow's and sheep's milk, pure albumins from hen's and duck's eggs, or corresponding proteins from plants of the same family. No chemist by identifying the nature and estimating the proportion of each amino-acid present can distinguish one member of such a pair from the other, but the anaphylactic reaction detects a difference where, until recently, chemistry was at a loss. There were those who supposed that the disparity depended on some physical difference in the structure of the colloidal solutions; others were ready to attribute it, not to the pure proteins, but to traces of associated lipoids; in both cases without any evidence.

There was always another possibility open, however, namely, that the antigenic individuality depended not merely on the nature and preparation of the amino-acids in the molecule, but on the order of their arrangement into the intricate molecular pattern. If one takes a heap of counters, comprising, say, a dozen different colors, with many of each color, it is possible to make an enormous number of different color patterns, without varying the number of colors or the proportions in which they are represented. Similarly, it is possible to imagine an almost endless variety in the intimate pattern of the protein molecules which can be constructed from the same

amino-acids in the same relative proportions. Only in the last few years has it become possible, through the work of Dakin and Dudley, to obtain some insight into the existence of this type of structural difference among proteins. With the single exception of glycine, all the amino-acids are constitutionally asymmetrical substances and exist in the protein molecule in the optically active form. The whole protein molecule, accordingly, is optically active, rotating the plane of polarised light. Kossel had shown that, under certain treatment, this optical activity of a native protein was gradually reduced to a steady minimum, and a first indication of the close relation between antigenic properties and the stereochemical structure was obtained, when Ten Broeck took such racemised egg-white, which Dakin and Dudley had prepared by Kossel's method, and found that it neither caused any sensitiveness in a guinea-pig, nor provoked any anaphylactic reaction in a guinea-pig rendered sensitive to the normal unracemised protein. Dakin and Dudley had already found that racemised protein was completely resistant to proteolytic ferment. It behaved in the body, indeed, not like a protein at all, but like a completely inert and indifferent material.

When such a racemised protein is hydrolysed into its constituent amino-acids, it is found that many of the amino-acids have been racemised completely, but that some retain partly or wholly their native optical activity. From a study of the behavior of certain analogous complexes, Dakin found reason for believing that the groups thus escaping racemisation are those which form the terminal links of the peptide chains out of which the molecule is built.

Here, then, was a method for obtaining a first hint as to the existence of structural difference between otherwise indistinguishable proteins. Dudley and Woodman first applied it to the caseins of cow's and sheep's milk, and found that, while these two proteins consist of the same amino-acids in identical proportions, the groups remaining optically active, when the whole protein is racemised as far as possible, are not identical in the two cases. The difference was small, but definite. It seemed desirable to repeat this comparison on two corresponding proteins having pronounced antigenic properties, and Dr. Dakin and I arranged a joint experiment. Similar proteins were to be taken from different species; Dakin undertook a comparison of their structure, in so far as his method would reveal it, while I undertook to investigate their antigenic specificity by the anaphylactic reaction. We chose the crystalline egg-albumins of the hen and the duck, partly because they were easily obtained pure, but chiefly because some preliminary experiments by Hartley and myself had appeared to indicate that they were indistinguishable, even by the anaphylactic reaction. Dakin, however, found a clear indication of difference in the order of arrangement of the amino-acids in the two albumins, and, on making more thorough and careful experiments on their antigenic properties, with samples of the pure products used by Dakin for his analysis, I found that the anaphylactic reaction distinguished clearly between them, though not with

absolute specificity. Table I summarizes the results of Dakin's examination of the changes in optical rotation of the individual amino-acids, when the two albumins were racemised.

TABLE I

Amino-acid	"Racemised" hen albumin	"Racemised" duck albumin	Comments
Alanine (1).	Not racemised.	Not racemised.	No difference.
Valine (2).	Partly racemised.	Partly racemised.	"
Leucine (3).	Mostly racemised.	Mostly active.	A definite difference.
Proline (4).	"	Mostly racemised.	No difference.
Phenylalanine.	Completely inactive.	Completely inactive.	"
Tyrosine (5).	Inactive.	Inactive.	"
Aspartic acid (6).	Mostly inactive, some active.	Completely inactive.	Definite difference.
Glutamic acid.	Completely inactive.	"	No difference.
Histidine (7).	"	Mostly active.	Definite difference.
Arginine.	Active.	Active.	No difference.
Lysine ( $\zeta$ ),	Inactive.	Inactive.	"

(From Biochemical Journal, Vol. XIII, p. 250)

Fig. 3 shows the response of the isolated uterine plain muscle of a guinea-pig, sensitized by a preliminary injection of hen albumin. It will be seen that it is indifferent to 2 milligrams of duck albumin, but responds by maximal tonus to 0.1 milligram of hen albumin, to which it is thereafter completely

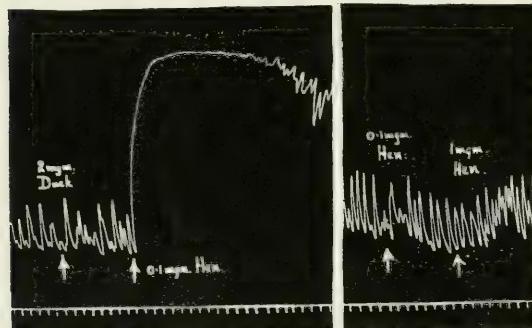


FIG. 3.—Sensitized with 1 mgm. of hen albumin. 21st day. (Dakin and Dale, Biochemical Journal, Vol. XIII, p. 253, Fig. 1.)

desensitized. Figs. 4 and 5 show similar experiments on the two horns of the uterus of a guinea-pig similarly sensitized to duck albumin. It will be seen (Fig. 5) that there is, in this case, a small response to 2 milligrams of hen albumin, but a subsequent maximal response to 0.1 milligram of duck albumin. The sensitization is not absolutely specific but very highly preferential. The reactions make a perfectly clear but not absolute distinction between the two proteins.

It is obvious that Dakin's method does not reveal the whole of the difference in structure which may exist between the two molecules. We are given, as it were, an imperfect glimpse of the edge of the pattern; but a difference already visible in such a partial view is the more significant. The window thus opened is in itself a small one, but it looks on a wide vista of possibilities.

I think we are entitled to hope that it will eventually be possible to state antigenic specificity in terms of structural

chemistry, to obtain a clear view of the intimate molecular pattern which gives to the protein its individuality, and of

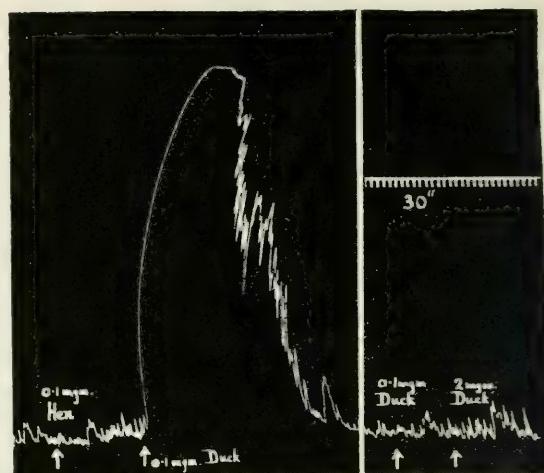


FIG. 4.—First horn. Sensitized with 1 mgm. of duck albumin. 28th day. (Dakin and Dale, Biochemical Journal, Vol. XIII, p. 254, Fig. 3.)

which the relation to a particular antibody has hitherto been the only indication. Perhaps it is not beyond reasonable hope that the antibody also may be obtained in sufficient purity

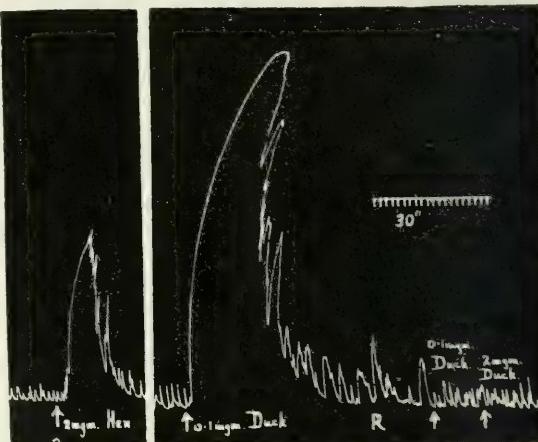


FIG. 5.—Second horn. (Dakin and Dale, Biochemical Journal, Vol. XIII, p. 255, Fig. 4.)

for such investigation of its structure as will enable us to replace, by a rational conception, the pictorial schema of its relation to the antigen, which Ehrlich displayed in the side-chain theory.

As to the nature of that relation, I think it must be admitted that exact knowledge is, as yet, almost entirely wanting. We are dealing with substances of very great molecular dimensions, and these molecules are so aggregated that they form typical colloidal solutions. It seems inevitable that surface phenomena will play a part in their interaction and formation of compounds, and may well impose upon the union quantitative relations which, viewed by themselves, would give to the whole process the aspect of an adsorption. But any such purely physical hypothesis will be inadequate. There has been an attempt to arrive at a simple electro-chemical conception of the union between antigen and antibody, representing it as the discharge and mutual precipitation of oppositely charged amphoteric colloids. Without denying the possibility that such a process may participate in some kinds of immune reaction, it is evident, I think, that these simple physical conceptions fail altogether to account for that specificity of discrimination, that exquisite adjustment of the antibody to a particular structure of the antigen molecule, which is the characteristic and essential feature of the relation. On the other hand, the existing chemistry does not enable us to account for this on purely chemical lines. It is hardly credible that it should involve a chemical combination in the sense of a synthesis by replacement. It must rather belong to the type of those molecular combinations, the dividing line between which and adsorption compounds is at present but ill-defined. We can go little further as yet than the citation of imperfect analogies. We have, for example, the relation of an enzyme to its substrate, again intimately dependent on the structure, and on the optical asymmetry of the substrate molecule, but presenting features which make it practically certain that surface phenomena play a part in bringing the two into relation. The analogy, however, is by no means a close one; it presents no parallel to the nicety of specific adjustment of the antibody to the antigen.

There is another comparison which, in this direction, shows us a more suggestive similarity, and which almost forces itself on the attention of any one who has been concerned with both types of investigation; namely, that between this union of antigen and antibody and the relation of certain classes of drug substances to the tissues or organs on which their action is specifically localized. You will remember that a comparison and contrast of the action of antigens with that of drug substances played a prominent rôle in the genesis of that wonderful fabric of theory with which Ehrlich so largely influenced the form and direction of research in pathology and pharmacology for almost a generation.

Nothing is further from my intention than to attempt here a survey of the enormous body of work and speculation which has been devoted to this ultimate pharmacological problem, of the relation between the chemical structure of a substance and its pharmacological action. It appears to me that we must recognize the improbability that the whole of the widely different types of activity of chemical substances will ever be brought under one principle of interpretation; indeed, I believe that progress towards rational conceptions has been

definitely retarded by attempts to force all kinds of pharmacological action under schemes of explanation which are found to have some application to one type in particular. For example, the relation between the activity of a large group of narcotic and anaesthetic substances and their solubility in fats and lipoids was realized by Ehrlich and presented with much suggestive detail of evidence by Meyer and by Overton. The significance once generally accorded to the high partition coefficient of these substances for lipoids, as compared with water, has been weakened by later evidence showing a similar relation between their narcotic action and other physical properties—their effect in lowering the surface tension of water, in aggregating protoplasm, in affecting the rate of gelation of certain colloidal systems, and so on. Possibly some of these may prove to be different aspects of the same fundamental property. There is evidence pointing to adsorption, as well as preferential solution in lipoids, as playing an important part in the concentration of these substances out of the blood into the cells whose activity they depress. But, whatever may be the ultimate conclusion as to the exact mechanism of the action of substances of the class of alcohol, chloroform, ether, I think it is reasonable to expect that it will be found to have a relatively simple physico-chemical basis.

There has been some danger, however, lest such simple physical conceptions should be given a width of application which the evidence will not justify; lest they should be invoked, with a facile vagueness, in explanation of certain types of activity which are characterized by an extraordinary precision of localization and a close dependence on certain types of chemical structure. It is here that we encounter, as it seems to me, many suggestive points of analogy with the relation between antigen and antibody, and it is of a few examples, which happen to have come within the scope of investigations in which I have taken part, that I wish now to speak.

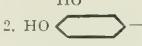
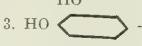
The types of action which I propose to mention are all exhibited by alkaloids and organic bases. No neutral or acidic substance, to my knowledge, has been shown to have a strictly localized action of the type I have in mind. The localization is so limited and exact that the action affects only certain functions of cells receiving their innervation from a particular morphological division of the nervous system.

An early example of such a precisely localized action was the paralyzing effect of curare, located at the end plates, where motor nerve-fibres end on skeletal muscle-fibres. Fraser and Crum Brown showed the close association between this type of action and the structural type of the quaternary ammonium-base. The parallel, however, is not complete; there are other substances than ammonium bases which have a curare-like action, such as cobra-venom; and there are certainly ammonium bases having a different type of action, resembling that of nicotine, which has a stimulant action localized on ganglion cells and, in varying degrees, on skeletal muscle fibres, and which, as Langley has shown, in general stimulates where curare paralyzes. Then there was the peripheral paralysis by atropine and hyoscine, and by many artificial esters of tropine, of the effects of nerves belonging to the cranial division

of the involuntary or autonomic system—the vagus, the chorda tympani, the short ciliary nerves; and the stimulant effects of pilocarpine, arecoline and muscarine, localized exactly where atropine and hyoscine paralyze.

Interest in such localized actions received a great impetus when it was discovered that an alkaloid occurring naturally in the body, and secreted continuously into the blood, the hormone-alkaloid epinephrine, had an action thus localized with extraordinary precision, as indicated by Lewandowsky and Langley, and demonstrated with a wealth of detailed evidence by Elliott and many later workers. The action of epinephrine, strictly localized at the periphery, reproduces with remarkable fidelity the action of nerves of the true sympathetic system and of no others, augmenting where these augment, inhibiting where they inhibit, and leaving altogether unaffected involuntary muscle and gland cells having no true sympathetic nerve-supply. It does not act on the nerves, since its action survives and is even intensified by complete degeneration of these to their ultimate visible terminations; nor does it act directly on the contractile or secretory elements in the effector organ, since its action is extinguished by the action of certain poisons, which also block the passage of impulses from sympathetic nerves, but leave the muscle or gland cell normally responsive to other kinds of stimuli, whether nervous or chemical. Such poisons render the muscle or gland cell irresponsible to sympathetic nerve impulses and to epinephrine, but leave them in other respects normal. Atropine similarly renders cells specifically indifferent to pilocarpine or muscarine. There is one such poison which differentiates function even more finely, eliminating the motor effects of sympathetic nerves and of epinephrine, but leaving the cells responsive to their inhibitor actions and to both motor and inhibitor stimuli of other kinds. This is the alkaloid of ergotoxine, the first of the pharmacologically interesting substances yielded by ergot, and the only one peculiar to it. There was at one time a tendency to cut the knot of the problem presented by the resemblance between the action of epinephrine and the effects of sympathetic nerves, by boldly assuming that the nerves of this system produce their effects by liberating epinephrine at their peripheral terminations. And certainly it is remarkable that a substance produced from the cells of the suprarenal medulla, which embryologically have the same origin as sympathetic ganglion-cells, should have its action localized on structures in which the axons of those ganglion-cells terminate at the periphery. But we are reminded of the theory which would explain the anaphylactic shock by the liberation of some substance of the histamine type. As in that case the pathologist, in this the physiologist seeks to get rid of his problem by reducing it to terms of pharmacology. Again, however, it seems to me that this merely shifts the incidence of the difficulty, without in the least degree removing it. It does not tell us why epinephrine, and, as we shall see, substances resembling it more or less closely in structure, when injected into the general circulation, have their action localized at the peripheral distribution of sympathetic-nerve fibres. We must suppose that there is some

structure which acts as transmitter between nerve fibre and contractile or secretory element, which determines the effect of the nerve impulse in the direction of augmentation or inhibition; and that in this myoneural or cytonerual junction there is some substance having a specific affinity for epinephrine and for substances of similar structure. Our problem is to discover what can be known of the nature of such a substance, and of the nature of its affinity for these bases.

- HO  Epinephrine.
- HO  From tyrosine.
- HO  From phenylalanine.
- CH<sub>3</sub>  From leucine.

I have written here the formulæ of six substances exhibiting in greater or less degree this epinephrine-like action, which Bayer and I termed "sympathomimetic" action. No. 1 is epinephrine itself; 2 is a synthetic compound from which epinephrine can be made artificially by reduction; 3 is also an artificial product of synthesis; the rest are bases derived, like histamine, from amino-acids, and therefore formed by the action of certain bacteria on products, and found in ergot and other fungi.

What is to be learned from a series like this, as to the nature of the affinity which so specifically localizes their action?

I do not think the conception of a specific solvent, extracting these bases preferentially from the blood, can really help us here. The lower members of the series are perfectly miscible with water, but can be extracted from it by organic solvents, in which they are even more soluble. Epinephrine and its immediate homologues are curiously insoluble in practically all neutral solvents. There are intermediate terms between these extremes of the series, but there is nothing to indicate a gradation of activity corresponding to any special kind of solubility. Nor is there any other physical property which appears to show any parallelism with activity.

There is, again, no kind of chemical reactivity which seems to be graded in the series in accordance with intensity of action. Reducing action has been mentioned as a characteristic chemical property of epinephrine, and attention has been drawn to the increase of both physiological activity and reducing action in passing from the ketones to the alcohols, as from 2 to 1 in the series given above. But there is another change effected in reducing the ketone to the alcohol, which has probably greater significance, namely, the introduction of an asymmetrical carbon atom and the production of an optically active compound. The reducing action of the ketones can be

similarly augmented by introducing a third phenolic hydroxyl, making a pyrogallol derivative, but this is slightly less, instead of much more, active than the parent catechol derivative; also it has still an optically symmetrical structure.

The only strictly chemical property common to all these substances is that they are bases. I think it is quite likely that this property is related to the fact that they are physiologically active on the cells in which they become locally concentrated. But for the reason of this localization and concentration, on which the specific nature and intensity of the action must primarily depend, we must look elsewhere.

I think there is no escape from the conclusion that the action is not associated with any physical characteristic or type of chemical reactivity which present knowledge enables us to appreciate or measure *in vitro*. It is associated rather with a type of chemical structure which gives to the substance a specific relationship to some substance in the myoneural junction; a relationship which becomes increasingly specific as the structure of epinephrine is approached. Again, as in the relation of antigen to antibody, we seem to be concerned with a relation of which the basis is chemical, as shown by its intimate dependence on structure, which cannot, however, be regarded as the synthetic formation of a new firm compound by replacement; which must be some looser type of additive molecular combination. Since we are dealing with concentration in, or on, the surface of living cells, we are dealing with a complex colloidal system, and it is highly probable that surface phenomena play a part. But, if we regard the relation as an adsorption, it must be an adsorption of a highly specific kind, closely dependent on the chemical structure as well as the physical nature of the surfaces concerned. Of such an adsorption, specifically conditioned by chemical structure, the physical chemist at present can tell us almost nothing. We are again in the borderland between chemical and physical union, the exploration of which holds out such promise for the illumination of biological conceptions.

Passing down the series as I have written it above, we see how a relationship, most intense and specific in the case of epinephrine and its immediate homologues, gradually becomes weaker and less specifically localized as one group after another is removed from the epinephrine molecule. In passing from epinephrine 1 to 2 or 3 the alcoholic hydroxyl of the side chain goes, optical asymmetry disappears and the action is weakened. In the lower members of the series the methyl group has disappeared from the amino-radical, and in these simpler compounds its absence seems to make no material difference to the activity. It is otherwise in the case of 1, 2, and 3. The primary amine corresponding to epinephrine, but having  $-NH_2$  in place of  $-NHCH_3$ , has a more powerful pressor action than epinephrine itself, and the same is true of 2 and its primary homologue; on the other hand the primary amine corresponding to 3 is much less active than the latter. It is a point of curious interest that the  $-NHCH_3$  compound is in all cases much more potent in reproducing *inhibitor* sympathetic effects.

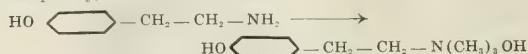
These relations, however, are rather too complex for our present purpose, which is to note how with successive departures from the epinephrine structure, removal of first one phenolic hydroxyl (in 4), then of the second (in 5), and lastly with disappearance of the benzene ring (in 6), we find a progressive weakening of the sympathomimetic action and progressive lessening of its specificity. Larger and larger doses are needed to evoke the characteristic effects, and they are more and more complicated by effects of other types. No. 6 has hardly any longer a perceptible resemblance to the epinephrine structure; it is, as it were, a mere featureless stump from which the characteristic outlines have been cut away. It still has a very definite sympathomimetic action, though weak and poorly specific. If we adopt Emil Fischer's comparison of the relation between enzyme and substrate as the fitting of a key into a lock, we may say that, in this series, as each ward is filed off the key, the fit becomes ever looser; it turns the lock with increasing difficulty and begins to fit others, though not well.

Keeping to the figure for a moment—and remembering that it is nothing more than a diagram—we may inquire what happens if, instead of removing wards, we add an excrescence to those present. Apparently we may destroy the fit of the key entirely. As the phenolic hydroxyls are removed we have seen that the activity becomes weaker and less specific; if they are methylated, replacing  $HO-$  by  $CH_3O-$ , the activity disappears completely.

The comparison with the relation of an enzyme to its substrate is rendered the more apposite by the discovery that the optically opposite forms of an asymmetrical compound, like epinephrine itself, differ very widely in their activities. Cushny found the natural *l*-epinephrine to be many times as active as the artificial *d*-epinephrine, just as he had found a similar difference of activity between the two hyoscamines, and more recently between the two hyoscines. Similarly Dakin showed, many years ago, that, of two optically isomeric mandelic esters, both were hydrolyzed by a lipase, but one with much greater rapidity than the other. He interpreted this result as indicating that the enzyme was itself asymmetrical and formed additive compounds with the two isomers, which would not then be optical antipodes. Cushny has similarly suggested the probability that the receptive substance, which localizes the action of an optically active drug-substance, is itself asymmetrical in structure. Whether the greater activity of *laevo*-epinephrine should be attributed to its more rapid entry into molecular combination with this substance, or to the more rapid occurrence of some consequent change, as Dakin suggested in the cases of the hydrolysis of the mandelic esters, is a point on which we have no basis of evidence even for surmise.

Let me mention briefly another series of compounds, having an activity with an entirely different localization from that which we have been considering. I have mentioned already the classical observation of Crum Brown and Fraser as to the curare-like action of quaternary ammonium bases. If we make an ammonium base from any member of the epinephrine series, by completely methylating the amino-group,

we obtain not a curare action, but a powerful action combining effects of nicotine with those of muscarine, though these latter are but weakly represented. If we take, for example, No. 4 of the above series (tyramine) and methylate its amino-group completely,



we obtain a quaternary ammonium base which has no longer a sympathomimetic action, but in its place a powerful stimulant action on autonomic ganglion cells and skeletal muscle fibres, closely resembling that of nicotine, and in addition a weaker peripheral action of the muscarine type, related to innervation, not by sympathetic nerves but by nerves of the other divisions of the autonomic system. We see a new significance in this change if we consider the molecule, as it were, from the other end, and realize that this quaternary compound may be regarded as a derivative of choline. It appears as No. 4 of the following series of derivatives of choline. Choline itself has, in a very weak form, both the nicotine and muscarine types of action, and both are intensified, in different degrees, by various forms of substitution of the alcoholic hydroxyl.

1. HO(CH<sub>3</sub>)<sub>2</sub>N—CH<sub>2</sub>—CH<sub>2</sub>—OH      Choline.
2. HO(CH<sub>3</sub>)<sub>2</sub>N—CH<sub>2</sub>—CH<sub>2</sub>—OC—CH<sub>3</sub>      Acetyl-choline.
3. HO(CH<sub>3</sub>)<sub>2</sub>N—CH<sub>2</sub>—CH<sub>2</sub>—ONO      Nitroso-choline ("synthetic muscarine").
4. HO(CH<sub>3</sub>)<sub>2</sub>N—CH<sub>2</sub>—CH<sub>2</sub>— OH      Trimethyl tyramine.
5. HO(CH<sub>3</sub>)<sub>2</sub>N—CH<sub>2</sub>      Tetramethyl ammonium hydrate.

In No. 2, acetyl-choline, the muscarine-like action is of unparalleled intensity, as shown by Reid Hunt and myself. The dose which will cause a perceptible fall of arterial pressure in a cat is of the order of 10<sup>-8</sup> milligram. The substance, however, is so rapidly hydrolysed in the body that the action of even larger doses is extremely evanescent. No. 3 has so pronounced a muscarine-like action that it was long believed to be an artificial muscarine, till Ervins and I showed that the action of nitric acid on choline is not to oxidize it but to form this nitroso-compound. Both 2 and 3 possess also a nicotine-like action, much more powerful than that of choline, but normally masked by their predominant muscarine effect. In 4 the nicotine-effect becomes predominant.

Again we are at a loss to relate the independent variation of these two types of action to any recognizable chemical or physical properties; and again we find them recognizable in the simplest remnant, as it were, of the molecule. No. 5, tetramethyl ammonium hydroxide, with the side chain reduced to an additional methyl group, still has both types of action, the nicotine action with great intensity. And in further illustration of the difficulty of the problem, let me draw your attention to the remarkable contrast between the action of this substance and its tetra-ethyl homologue, HO(C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>N. In all ordinary chemical and physical properties the tetramethyl and tetra-ethyl ammonium salts are practically identical. Yet the tetramethyl ammonium salts have these two types of activity, those of muscarine and nicotine, strongly developed, while the tetra-ethyl ammonium salts have them not at all.

The intermediate compounds, with methyl and ethyl groups in varying proportions, show these actions in proportion to the number of methyl groups present. Again we are driven back on a conception of some peculiar conformation of the reactive surfaces to which the methyl groups are adjusted, which the ethyl groups will not fit.

A few years ago, in discussing this curious contrast between the methyl and ethyl ammonium bases, I ventured to say that it was as mysterious as the physiological contrast between sodium and potassium. Since that rash comparison was committed to print, the peculiar physiological position of potassium has been illuminated from an altogether unexpected quarter. Zwaardemaker has revealed its relation to the scarcely noticed fact that potassium is a weakly radioactive element. The key to the problem we have been discussing may not be found as suddenly, but I think it is not improbable that there are factors concerned in determining the activity of some of the organic compounds we have been considering, the importance of which is as little appreciated as was that of the radioactivity of potassium but a few years ago. This feeling, that we are always on the verge of some great clarification, is, I believe, a powerful element in the fascination which this problem of the relation between action and constitution has exercised on many minds. We have plenty of stimulating suggestions and seductive analogies—half-lights and elusive hints. Progress towards real clarity of conception can only come from the continuous co-operation and intercourse between the workers in all the different departments of scientific inquiry with which the problem makes contact. Particularly, I think, is it necessary to realize that the core of the problem is physiological. We have had big books on the subject, of great value as works of reference, written by chemists who were content to take their biological data at second or third hand, from sources of the most variable authority and who have extracted from such materials generalizations as to the function of particular groupings. We find, for example, a statement copied from one to another compilation of this kind, that nicotine and pilocarpine are closely similar in action, and that this is related to the presence in each of a five-membered ring. The real problem is created by the fact that the action of pilocarpine closely resembles, not that of nicotine, but that of muscarine and arecoline, and that no one hitherto has traced any structural or other similarity between these three; and that nicotine resembles in its action not pilocarpine, but lobeline and cytisine, which, again, have not been shown to have any other point of definite community with it. We need all the help that organic and physical chemistry can give, but the initiative and the guiding influence in the inquiry must come at least as much from the physiological side. Under such conditions I believe the quest is well worthy of an eager pursuit. It is not merely a question of finding a scientific basis for the production of more and better therapeutic agents than those which are yet available. There is a whole group of physiological and pathological problems here closely knit together, and, from whatever quarter the light comes, it cannot fail to illuminate the whole field.

# BULLETIN

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## THE EFFECT OF DIPHTHERIA ANTITOXIN IN PREVENTING LODGMENT AND GROWTH OF THE DIPHTHERIA BACILLUS IN THE NASAL PASSAGES OF ANIMALS

By J. GELIEN, W. L. MOSS AND C. G. GUTHRIE, M. D.

(From the Research Laboratory, Phipps Tuberculosis Dispensary, Johns Hopkins Hospital)

The value of antitoxin as a curative agent in the treatment of diphtheria has been proven beyond all doubt. Its efficacy, also, in the prophylaxis of the disease is so well known as to need no comment, except that the immunity conferred by it is relative, passive, and exerted over a short but variable period. On the other hand, the desirability of its prophylactic use is, perhaps, questionable and a subject which merits further consideration. Whether used as a curative or preventive agent, its action depends upon its ability to neutralize the circulating toxin elaborated by the diphtheria bacillus. This action is purely antitoxic, not bactericidal, but apparently this fact is not infrequently overlooked, although supported by abundant experimental and clinical evidence. Diphtheria bacilli may persist in the nose and throat of an individual for weeks and even months after all clinical manifestations of the disease have disappeared, despite the oft repeated injection of antitoxin subcutaneously. Likewise, the local use of antitoxin in the pharynx and nares is without effect, other than the mechanical cleansing which might be accomplished as well, perhaps, with salt solution. Doubtless negative cultures are sometimes obtained after local treat-

ment with antitoxin, but *post hoc* is not necessarily *propter hoc*, and we have seen cases that resisted it for weeks, although administered by firm believers in this method of eradication. It has been our observation that Klebs-Loeffler bacilli may disappear from the nose and throat of those recovering from diphtheria following the employment of various other local measures or may persist in spite of any or all such medication. On the other hand, they may vanish spontaneously without assistance from the physician. Such observations, together with a considerable series of unpublished experiments on animals with regard to this point, have led us to question the value of the forms of local treatment so far proposed for this purpose. If one may judge from experiments *in vitro*, there is no reason to suppose that antitoxin has any virtue as a local agent since the diphtheria bacillus grows luxuriantly in it.

Another rather important aspect of the antitoxin question is usually overlooked or dismissed with a few words. This concerns its effect in preventing the lodgment and growth of the diphtheria bacillus in individuals receiving prophylactic injections. In order to throw some light on this point, the

animal experiments which form the basis of this report were undertaken.

*Object.* To determine whether antitoxin administered subcutaneously will prevent the subsequent lodgment and growth of diphtheria bacilli in the naso-pharynx.

*Procedure.* Guinea-pigs, rabbits and cats were the animals employed and the general plan of procedure was as follows. Preliminary cultures were made on all the animals to show that they were free from diphtheria bacilli at the beginning of the experiments. The animals used in each experiment were divided into two groups, one of which received antitoxin subcutaneously, the other group serving as a control, without antitoxin. Subsequently both groups were exposed equally to infection with diphtheria bacilli. In one series of experiments this exposure consisted in the introduction of diphtheria bacilli into the naso-pharynx by means of a swab. In others an attempt was made to imitate more nearly natural conditions. This consisted in caging both groups—that which had received antitoxin and that which had not)—with a "carrier" animal. At the outset it was intended to follow the animals throughout the investigation by means of throat cultures, but we soon found that nasal cultures were more practicable and more satisfactory. Tiny swabs were made by winding a small wisp of cotton about the coarser and stiffer end of pig bristles. After a little practice it was found quite simple to introduce a swab by way of the nostril into the posterior nares. Cultures were made on Loeffler's blood serum and examined after 15 or 20 hours in the thermostat. Diphtheria bacilli were isolated from a large percentage of the positive cultures and the result of the primary examinations confirmed. Preliminary cultures showed that all of the animals used were free from diphtheria organisms before inoculation. As will be indicated when the experiments are taken up in detail, certain of the animals were subjected to nasal inoculation with *B. diphtheriae* from time to time. These inoculations were made by introducing into the posterior nares a swab which had been soaked in a thick, opaque suspension of diphtheria bacilli. Two strains of organisms were used which were obtained from the throats of school children during the course of a previous investigation. Both were typical in mor-

phology and cultural characteristics, but one (1157) was virulent and the other (1032) was avirulent.

After preliminary nasal culture of all the animals they were divided into groups of 10, with the exception of those used in Experiments VII and VIII, which consisted in each instance of a cat with five kittens. Each group was kept in a separate floor cage, sufficiently large to avoid overcrowding and removed as far as was possible from the other groups. One half of the animals in each group received diphtheria antitoxin beneath the skin of the abdomen, 250 units being the individual dose. This was followed next day by nasal inoculation of all animals in Series A (Exp. I, II and III) and by the introduction into each group of Series B (Exp. IV, V, VI, VII and VIII) of a "carrier" animal which that day received artificial nasal inoculation with diphtheria bacilli. Nasal cultures were then taken at two-day intervals. It soon became apparent that the initial inoculation with diphtheria bacilli had been insufficient or ineffectual, as in some of the groups no positive cultures were found for six days thereafter. For this reason the injection of antitoxin was repeated and in the afternoon of the same day the animals were re-inoculated. On this occasion, thicker suspensions of bacteria were used and the infected swabs were allowed to remain in the nose for a longer time than at the primary inoculation. The nasal cultures at intervals of two days were resumed and a much higher percentage of positive results obtained.

A few words with regard to the fate of the 70 animals used in this work may not be inappropriate here. None of them developed signs or symptoms of diphtheria, and those that died showed no evidence of this disease. The guinea-pigs and rabbits remained healthy, with one exception (R. 219, Exp. V), and were in a thriving condition at the conclusion of the experiments. Among the cats, however, there was a high mortality, owing to the prevalence of distemper\* and the difficulty in keeping these animals healthy in confinement.

The list of experiments in detail, with the results obtained is shown in Series A and B.

\* "Distemper" is merely used as a convenient term for the disease characterized by sore eyes, snuffles and bronchopneumonia.

#### SERIES A

**EXPERIMENT I.**—Nasal cultures from ten guinea-pigs. All having artificial nasal inoculation with avirulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i>		Result of culture 1	Result of culture 2	Result of culture 3	Result of culture 4
			July 1	July 2				
G.-P. 12...	0	250 units	Yes	0	0	250 units	Yes	+
13...	0	" "	"	0	0	" "	"	0
14...	0	" "	"	0	0	" "	"	0
15...	0	" "	"	0	0	" "	"	0
16...	0	" "	"	0	0	" "	"	0
17...	0	None	"	0	0	None	"	0
18...	0	"	"	0	0	"	"	0
19...	0	"	"	0	0	"	"	0
20...	0	"	"	0	0	"	"	0
21...	0	"	"	0	0	"	"	0

## SERIES A—CONTINUED

EXPERIMENT II.—Nasal cultures from ten rabbits. All having artificial nasal inoculation with virulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture 1	Result of culture 2	Result of culture 3	Result of culture 4	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture 5	Result of culture 6
	June 27	June 27	June 28	June 30	July 2	July 4	July 6	July 6	July 6	July 8	July 10
R. 210.....	0	250 units	Yes	0	0	0	+	250 units	Yes	+	0
230.....	0	" "	"	0	0	0	0	" "	"	0	0
225.....	0	" "	"	0	0	0	0	" "	"	0	0
235.....	0	" "	"	0	0	0	0	" "	"	0	0
220.....	0	" "	"	0	0	0	+	" "	"	0	0
234.....	0	None	"	0	0	0	0	None	"	0	0
214.....	0	"	"	0	0	0	0	"	"	+	0
223.....	0	"	"	0	0	0	0	"	"	0	0
236.....	0	"	"	0	0	0	0	"	"	+	0
226.....	0	"	"	0	0	0	+	"	"	+	0

EXPERIMENT III.—Nasal cultures from ten cats. All having artificial nasal inoculation with avirulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1032)	Result of culture 1	Result of culture 2	Result of culture 3	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1032)	Result of culture 4	Result of culture 5	Result of culture 6
	June 28	June 28	June 29	July 1	July 3	July 5	July 6 A. M.	July 6 P. M.	July 7	July 9	July 11
C. 1....	0	250 units	Yes	0	0	0	250 units	Yes	+	0	0
2....	0	" "	"	+	0	0	" "	"	0	0	0
3....	0	" "	"	+	0	0	" "	"	0	0	0
4....	0	" "	"	0	0	0	" "	"	0	0	+
5....	0	" "	"	0	0	0	" "	"	+	0	0
6....	0	None	"	0	0	0	None	"	+	0	+
7....	0	"	"	0	0	0	"	"	+	Dead	..
8....	0	"	"	0	0	0	"	"	+	0	+
9....	0	"	"	0	0	0	"	"	0	0	+
10....	0	"	"	Dead	..	..	..	..	..	..	..
34	0	"	"	+	0	0	"	"	+	+	+

C. 10 died June 30. Autopsy negative. C. 4 and C. 5 killed July 13. Autopsy negative except for pus in nose and inflammation of intestines. C. 7 died July 8. Intestinal symptoms. C. 34 substituted for C. 10, July 1.

## SERIES B

EXPERIMENT IV.—Nasal cultures from 11 guinea-pigs. One having artificial inoculation with virulent diphtheria bacilli. Ten not having artificial nasal inoculation with virulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture 1	Result of culture 2	Result of culture 3	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture 4	Result of culture 5
	June 28	June 28	June 29	July 1	July 3	July 5	July 6 A. M.	July 6 P. M.	July 7	July 9
G.-P. 1....	0	250 units	No	0	0	+	250 units	No	0	+
2....	0	" "	"	+	0	0	" "	"	0	+
3....	0	" "	"	0	0	0	" "	"	+	+
4....	0	" "	"	0	0	+	" "	"	0	0
5....	0	" "	"	0	0	0	" "	"	+	0
6....	0	None	"	0	0	+	None	"	0	0
7....	0	"	"	+	0	+	"	"	+	0
8....	0	"	"	+	0	+	"	"	+	+
9....	0	"	"	+	0	+	"	"	+	0
10....	0	"	"	0	0	0	"	"	0	0
11....	0	"	Yes	+	0	0	"	Yes	+	+

EXPERIMENT V.—Nasal cultures from 11 rabbits. One having artificial nasal inoculation with avirulent diphtheria bacilli. Ten not having artificial nasal inoculation with avirulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1032)	Result of culture 1	Result of culture 2	Result of culture 3	Result of culture 4	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1032)	Result of culture 5	Result of culture 6
	June 27	June 27	June 28	June 30	July 2	July 4	July 6	July 6 A. M.	July 6 P. M.	July 8	July 10
R. 219	0	250 units	No	0	0	0	0	250 units	No	+	Dead
233	0	" "	"	+	0	0	0	" "	"	0	0
231	0	" "	"	0	0	0	0	" "	"	+	0
224	0	" "	"	0	0	0	0	" "	"	+	0
222	0	" "	"	0	0	0	0	" "	"	0	0
237	0	None	"	0	0	0	0	None	"	+	0
226	0	"	"	0	0	0	0	"	"	0	0
227	0	"	"	0	0	0	0	"	"	0	0
128	0	"	"	0	0	0	0	"	"	0	0
216	0	"	"	0	0	0	0	"	"	..	..
228	0	"	Yes	0	0	0	0	"	Yes	+	0

R. 219 died July 10. Autopsy: Plastic pleurisy right side, plastic peritonitis.

## SERIES B—CONTINUED

EXPERIMENT VI.—Nasal cultures from 11 cats. One having artificial nasal inoculation with virulent diphtheria bacilli. Ten not having artificial nasal inoculation with virulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture	Result of culture	Result of culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture	Result of culture	
	June 29			June 30	July 2	July 4	July 6	July 6 A. M.	July 6 P. M.	July 8	July 10
C. 23.....	0	250 units	No		0	0	0	250 units	No	0	0
24.....	0	" "	"		Dead	....	....		....	....	....
25.....	0	" "	"		0	0	0	250 units	No	0	0
26.....	0	" "	"		0	0	0	Dead	....	....	....
27.....	0	" "	"		0	0	0	250 units	No	+	0
56.....	0	" "	"		0	0	0	" "	"	+	0
46.....	0	....	"		....	....	....	" "	"	0	0
28.....	0	None	"		0	0	0	None	"	0	0
29.....	0	"	"		0	0	0	"	"	0	0
30.....	0	"	"		Dead	....	....	....	....	....	....
31.....	0	"	"		0	0	0	None	No	0	0
32.....	0	"	"		0	0	0	"	"	0	0
42.....	0	"	"		0	0	0	"	"	0	0
33.....	0	"	Yes		0	0	0	"	Yes	+	0

C. 24 died July 2. Autopsy negative. C. 26 died July 6. C. 30 died July 1. Autopsy negative. Intestinal symptoms. C. 42 substituted for C. 30, C. 56 substituted for C. 24 and C. 46 substituted for C. 26.

EXPERIMENT VII.—Nasal cultures from six cats (mother and five kittens). Mother having artificial nasal inoculation with virulent diphtheria bacilli. Kittens not having artificial nasal inoculation with virulent diphtheria bacilli. Two kittens having previously received diphtheria antitoxin subcutaneously. Three kittens not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture	Result of culture	Result of culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1157)	Result of culture	Result of culture	Result of culture			
	June 28			June 28	June 29	July 1			July 3	July 5	July 6 A. M.	July 6 P. M.	July 7	July 9
C. 12....	0	250 units	No		0	0	0	250 units	No	+	+	+	+	+
13....	0	" "	"		0	0	0	" "	"	+	+	+	+	+
14....	0	None	"		0	0	0	None	"	0	+	+	+	+
15....	0	"	"		0	0	0	"	"	0	+	+	0	0
16....	0	"	"		0	0	0	"	"	+	+	+	+	+
11....	0	"	Yes		0	0	0	"	"	...	...	...	...	...
54....	0	....	....		...	...	...	"	Yes	+	+	+	+	+

C. 12  
13  
14  
15  
16  
kittens. { C. 11, mother cat escaped July 6.  
C. 54, female cat (lactating) substituted for C. 11, July 6.

## SERIES B—CONTINUED

EXPERIMENT VIII.—Nasal cultures from six cats (mother and five kittens). Mother having artificial nasal inoculation with avirulent diphtheria bacilli. Kittens not having artificial nasal inoculation with avirulent diphtheria bacilli. Three kittens having previously received diphtheria antitoxin subcutaneously. Two kittens not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture	Antitoxin subcutaneously	Nasal inoculation with <i>B. diphtheriae</i> (1032)	Result of culture 1	Result of culture 2	Result of culture 3
	June 28			July 1	July 3	July 5
C. 18.....	0	250 units	No	0	0	0
19.....	0	" "	"	0	Dead	....
20.....	0	" "	"	+	0	+
21.....	0	None	"	0	Dead	....
22.....	0	"	"	0	0	0
17.....	0	"	Yes	0	0	0
C. 18 19 20 21 22	kittens.	C. 17, mother cat. C. 19 died July 2. Autopsy. Sore eyes, pneumonia. C. 21, died July 1. Autopsy. Sore eyes, pneumonia.				

## ANALYSIS OF RESULTS OF EXPERIMENTS I TO VIII \*

		Number of animals				Total number of cultures			
		With antitoxin		Without antitoxin		Animals with antitoxin		Animals without antitoxin	
		Sometime pos. cult.	Always neg. cult.	Sometime pos. cult.	Always neg. cult.	Total pos. cult.	Total neg. cult.	Total pos. cult.	Total neg. cult.
Series A.....	Experiment I, organism avirulent (1032)...	3	2	2	3	3	17	2	18
	Experiment II, organism virulent (1157)...	2	3	3	2	3	27	4	26
	Experiment III, organism avirulent (1032)...	5	0	5	0	5	25	10	18
	Total.....	10	5	10	5	11	69	16	62
Series B.....	Experiment IV, organism virulent (1157)...	5	0	4	1	8	17	11	14
	Experiment V, organism avirulent (1032)...	4	1	1	4	4	25	1	26
	Experiment VI, organism virulent (1157)...	2	3	0	5	2	23	0	25
	Experiment VII, organism avirulent (1032)...	2	0	3	0	6	6	6	12
	Experiment VIII, organism virulent (1157)...	1	2	0	2	2	5	0	7
	Total.....	14	6	8	12	22	76	18	84
Series A and B..	Experiments I-VIII. Total.....	24	11	18	17	33	145	34	146
Series A and B..	Organism virulent (1157) Exp.IV, VI, VII, VIII.	11	6	10	8	19	73	21	77
	Organism avirulent (1032) Exp.I, III, V, VII.	13	5	8	9	14	72	13	69
	Total.....	24	11	18	17	33	145	34	146
Series A and B..	Guinea-pigs. Experiments I and IV.....	8	2	6	4	11	34	13	32
	Rabbits. Experiments II and V.....	6	4	4	6	7	52	5	52
	Cats. Experiments III, VI, VII and VIII ...	10	5	8	7	15	59	16	62
	Total.....	24	11	18	17	33	145	34	146

\* This table does not include the preliminary cultures which were made on all the animals, nor the results of cultures on the "carriers" in Series B, *vid., Exp. IV, G. P. 11; Exp. V, R. 228; Exp. VI, C. 33; Exp. VII, C. 11 and C. 54; Exp. VIII, C. 17.*

To this may be appended, for the sake of comparison, the cultural results obtained with a series of 40 animals used in other experiments. The animals were arranged in groups of 10 and, after preliminary cultures, all were inoculated in the same manner and with the same strains of bacteria as in the foregoing experiments. They, also, were cultured at two-day intervals and after each culture one half the animals in

each group were sprayed in the nose with killed cultures of *Staphylococcus aureus* or *B. pyocyanus*. Later, living cultures of these organisms were used but no beneficial effect, inhibitory or otherwise, could be noted as a result of the spraying. The results of the cultures are merely given to serve as a comparison with the figures given in the analyses of results of Experiments I to VIII.

## SHOWING RESULTS OF EXPERIMENTS IX TO XII

Experiment number	Number and kind of animal	<i>B. diphtheriae</i> used for inoculation	Organism used in spray treatment	Number of animals		Number of cultures	
				+	0	+	0
IX	10 rabbits .....	Avirulent (1032).....	Pyocyanus.....	7	3	10	33
X	10 cats .....	Virulent (1157).....	Pyocyanus.....	1	9	1	27
XI	10 rabbits .....	Avirulent (1032).....	Aureus .....	3	7	4	16
XII	10 guinea-pigs .....	Virulent (1157).....	Aureus .....	6	4	7	21
				17	23	22	97

## SHOWING COMBINED RESULTS OF EXPERIMENTS I TO XII

		Number of animals				Number of cultures			
		+	0	Total	% +	+	0	Total	% +
Experiments I to VIII (Series A and B).....		42	28	70	60%	67	291	358	19%
Experiments IX to XII (Aureus and Pyocyanus).....		17	23	40	43%	22	97	119	18%
Total.....		59	51	110	54%	89	388	477	19%
Guinea-pigs. Experiments I, IV and XII .....		20	10	30	66%	31	87	118	26%
Rabbits. Experiments II, V, IX and XI.....		20	20	40	50%	26	153	179	15%
Cats. Experiments III, VI, VII, VIII and X.....		19	21	40	48%	32	148	180	18%
Total.....		59	51	110	54%	89	388	477	19%

*Comment.* Certain conditions in these experiments with animals are quite different from those which obtain in human beings, notably the frequency with which the carrier state occurs spontaneously and the ease with which it may be produced experimentally.

In a large series of human beings including both children and adults, we found that a single examination revealed an incidence of diphtheria bacillus carriers of about 3.55 per cent. A second examination practically doubled the number of carriers discovered, while a third examination still further increased the original number. Among the 72 animals which form the basis of these experiments as well as the 40 additional animals referred to in the body of the paper none showed diphtheria bacilli at the beginning of the work.

We have been able to induce the carrier state in man experimentally both with virulent and with non-virulent diphtheria bacilli, not with regularity, it is true, but in a considerable proportion of a small series of individuals.\* In guinea-pigs, rabbits and cats, however, we found the carrier state difficult to produce and generally very transient if it occurred at all. The number of diphtheria bacilli present in the positive cultures, moreover, was very small as compared with the total number of organisms of various kinds which developed. This is a condition of affairs quite different from that commonly observed in cultures from human carriers and raises the question as to whether the diphtheria bacilli had actually multiplied or merely persisted in the nasal passages of these animals. On the basis of experience derived from work with these and other animals of the same kinds, we believe that those animals showing positive cultures at the last recorded observation would probably have become negative in a few days.

\* A detailed account of this work will appear in a later paper.

It is evident that the period covered by these examinations was too short. Observations over a longer time would have served, in all probability, to render the results more striking and clear cut. Despite these drawbacks, some facts seem apparent from the 358 cultures on 70 animals.

*Summary.* (1) The production of nasal infection or infestation of cats, rabbits and guinea-pigs with *B. diphtheriae* was quite inconstant even when the organisms were introduced directly into the nose.

(2) A somewhat higher percentage of animals showed positive cultures among those directly inoculated than among those merely exposed to a "carrier" (Series A, 66 per cent; Series B, 55 per cent). A much greater discrepancy would not have been surprising.

(3) Cats and rabbits became infected with about the same frequency (C., 48 per cent; R., 50 per cent) and the incidence of positive cultures was also much the same (C., 18 per cent; R., 15 per cent). Among the guinea-pigs, 66 per cent developed positive cultures and 26 per cent of the total number of cultures taken showed Klebs-Loeffler bacilli.

(4) The duration of infection was usually quite short but may have been variable in this respect, as some animals still harbored diphtheria organisms at the end of the experiments.

(5) The health of the animals was apparently unaffected by the mere presence of the bacilli in the nose.

(6) The occurrence and duration of infection were independent of the virulence of the strain of organisms used for inoculation and (7) were wholly unaffected by the previous administration of antitoxin.

#### CONCLUSION

The subcutaneous administration of antitoxin does not prevent the lodgment and growth of *B. diphtheriae* in the nasal passage of cats, guinea-pigs and rabbits.

## DIPHTHERIA BACILLUS CARRIERS SECOND COMMUNICATION<sup>\*</sup>

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#### PART I

The following brief summary gives the main facts brought out in our first communication, published in the Transactions

of the Fifteenth International Congress on Hygiene and Demography, 1912, IV, 156.

*Incidence of diphtheria bacillus carriers among presumably healthy persons as shown by a single examination of the throat.*

A single throat culture from each of 1217 school children revealed diphtheria bacilli in 44 instances, 3.61 per cent. A single throat culture from each of 1290 individuals in the city at large, most diverse as to age, sex, race and social position, showed diphtheria bacilli in 45 cases, 3.48 per cent. These two groups together make a total of 2507 individuals in the city of Baltimore during the spring of 1911, 89 of whom gave a positive throat culture, 3.55 per cent.

\* This investigation was made by authority of the Department of Health of Baltimore City, and it is a pleasure to make grateful acknowledgment of the hearty co-operation and valuable assistance of Dr. Jas. Bosley, Commissioner of Health, Dr. C. Hampson Jones, Assistant Commissioner of Health, Drs. R. A. Urquhart and I. R. Page, school physicians, and Mrs. H. E. Knorr, school nurse.

The cultures and examinations of the throats were made in all instances by Drs. Urquhart and Page. Mrs. Knorr visited each "carrier" in his or her home and made the most thorough and painstaking inquiry which forms, in large part, the basis of our report on the relation of the carrier to the community.

*Persistence of diphtheria bacilli in the throats of persons who gave a positive culture.* Forty-six of the school children who gave a positive culture at the first or second examination were re-examined after a lapse of 1½ to 3 months, and 10, or 21.74 per cent, again gave positive cultures.

*Virulence of the diphtheria bacilli present in the throats of children having positive cultures.* Diphtheria bacilli were isolated from 33 of the children having positive cultures and their virulence tested. Six, or 18.18 per cent, were found to be virulent.

*Relation of diphtheria bacillus carriers to the community.* The most important and striking feature of the investigation was the previous and subsequent history and the relation to the community with reference to clinical diphtheria of 49 school children having positive cultures. Of these 49 diphtheria bacillus carriers a history of previous clinical diphtheria could be obtained in only 3 (three, four and five years previously), a positive history of previous exposure was obtained in 3 (three, five and seven years previously), and a doubtful history of exposure, four years previously, in one. Not one of the 49 carriers subsequently, during the period of observation, developed clinical diphtheria, and a most careful investigation failed to reveal a single case of clinical diphtheria developing among any of the associates of these 49 carriers.

In discussing the results of this investigation, we pointed out that a single examination of any group of persons is not sufficient to determine the true incidence of carriers and it follows, of course, that a single re-examination is not sufficient to determine the question of persistence.

In order to throw more light on some of the questions raised in our first report and to extend our observations to cover some additional problems, we have undertaken a second investigation.\*

#### OBJECT

1. To determine the persistence of *B. diphtheriae* in the throats of persons having positive cultures but not suffering from clinical diphtheria.

2. To determine the virulence or non-virulence of the diphtheria bacilli present in the throats of such persons.

3. To determine whether the diphtheria bacilli growing in the throats of such persons may undergo a change in virulence; that is, whether a virulent one may become avirulent or an avirulent organism acquire virulence while growing in the throat of a carrier.

4. To determine whether any relation exists between the presence of diphtheria bacilli and pathological throat conditions other than clinical diphtheria.

5. To determine by history and observation whether:

(a) Any of the carriers investigated have at any previous time had clinical diphtheria.

\* In the various studies on diphtheria bacillus carriers and in the animal experiments in connection with them which we have made it has been necessary to use a large amount of diphtheria antitoxin. Antitoxin for this purpose was generously furnished us free of cost by the Lederle Laboratory and we desire to acknowledge with appreciation \$150.00 worth of antitoxin received from this source.

- (b) Any of them develop clinical diphtheria during the period they are under observation.
- (c) Any of them have ever been exposed to a case of clinical diphtheria.
- (d) Any one in contact with the carriers investigated develops clinical diphtheria.

#### PLAN FOR CARRYING OUT THE ABOVE INVESTIGATION

1. Fifty diphtheria bacillus carriers are to be selected and throat cultures made on them at intervals of two weeks for a period of three months.

2. At the time of each culture any obviously pathological condition of the throat, such as hypertrophied and infected tonsils, pharyngitis, etc., is to be noted and the temperature of the child recorded.\*

3. Each time a positive culture is obtained the diphtheria bacillus is to be isolated in pure state, tested for virulence and its cultural, morphological and tinctorial characteristics studied.

In order to secure 50 carriers for the purpose of this investigation a single throat culture was made on each of 800 children in School V (February 12, 13, 14 and 15, 1912). This was the school which had yielded the highest percentage of positive cultures in the course of our work in 1911. The name, age, sex, class and home address of the child and objective condition of the throat at the time of making the culture were recorded. From the children having positive cultures at this examination 50 were selected for repeated cultures according to the plan outlined above and at the end of three months a reculture was made of the original 800 children and pathological conditions of the throat again noted. Moreover, temperature observations were made on 431 of these children at the time of this examination.

The observations made on the 800 children, from whom the 50 carriers were selected, furnished data on some points not specifically set forth as the object of this investigation, but which it seems worth while to include in the report.

An analysis and summary of the results of the first examination of 800 children in School V, made February, 1912, is contained in Table I.

Examination of Table I shows that among 800 children 85 were found to have positive throat cultures, 10.62 per cent.

There were 426 males and 374 females. The incidence of positive cultures in these two groups was practically the same, 10.56 per cent among the males and 10.69 per cent among the females.

There were 221 children under eight years of age with an incidence of 11.31 per cent of positive cultures and 579

\* Great care was taken in this investigation to prevent any possibility of carrying infection from one child to another. In making the throat examinations a separate wooden tongue depressor was used for each child and afterwards burned. In taking the temperatures the thermometers were disinfected by being placed for five minutes in a 1:1000 solution of mercury bichloride each time before a temperature was taken.

children over eight years old with 10.36 per cent of positive cultures.

TABLE I

FIRST EXAMINATION OF 800 CHILDREN, SCHOOL V, FEBRUARY, 1912.  
ANALYZED WITH REFERENCE TO AGE, SEX, POSITIVE CULTURES AND PATHOLOGICAL THROATS

	Pos. cultures		Path. throats	
	Number	Per cent	Number	Per cent
800 children 4-17 years old.....	85	10.62	211	26.37
426 males .....	45	10.56	127	29.81
374 females.....	40	10.69	84	22.46
221 children under 8 years.....	25	11.31	75	33.93
579 children over 8 years.....	60	10.36	136	23.48
110 males under 8 years.....	11	10.00	48	43.63
111 females under 8 years.....	14	12.61	27	24.32
316 males over 8 years.....	34	10.75	79	25.00
263 females over 8 years.....	26	9.88	57	21.67

Males under eight years had a slightly smaller percentage of positive cultures than did the females under eight years: 10 per cent for males as compared with 12.61 per cent for females. Males over eight years, on the other hand, had a slightly higher percentage of positive cultures than did females over eight years of age; 10.75 per cent as compared with 9.88 per cent.

The above percentages are remarkable, not for their variation, but for their very great uniformity and they indicate that, in the children examined, there was practically no difference in the incidence of positive cultures in the various groups considered.

When we come to analyze the above table for pathological throat conditions we find wide variations between the sexes, at different ages, etc. The total number of throats noted as pathological in the 800 children examined is 211, or 26.37 per cent. More of these occur in males (29.81 per cent) than in females (22.46 per cent). More occur in children under eight years old (33.93 per cent) than in children over eight years old (23.48 per cent). Males under eight years old have the highest incidence of any group (43.63 per cent). Females under eight years have an incidence of 24.32 per cent. Males over eight years, 25 per cent. Females over eight years, 21.67 per cent.

We wish next to analyze the relationship which exists between pathological conditions of the throat and the occurrence of positive cultures and to determine, if possible, whether this relation is a causal one; and if a causal one, which is cause and which effect (see Table II).

If we compare in the various groups the incidence of positive cultures in pathological throats with the incidence of positive cultures in normal throats (Table II) we find:

	Per cent
In 211 children with path. throats 25 pos. cultures.....	11.84
In 589 children with normal throats 60 pos. cultures.....	10.18

TABLE II  
COMPARING THE INCIDENCE OF POSITIVE CULTURES IN CHILDREN HAVING PATHOLOGICAL THROATS AND IN THOSE HAVING NORMAL THROATS

	Positive cultures	
	Number	Per cent
211 children with path. throats.....	25	11.84
589 children with normal throats.....	60	10.18
127 males with path. throats.....	13	10.23
299 males with normal throats.....	32	10.70
84 females with path. throats.....	12	14.28
290 females with normal throats.....	28	9.65
75 children under 8 years path. throats.....	12	16.00
146 children under 8 years normal throats.....	13	8.90
136 children over 8 years path. throats.....	13	9.55
443 children over 8 years normal throats.....	47	10.85
48 males under 8 years path. throats.....	5	10.41
62 males under 8 years normal throats.....	6	9.67
27 females under 8 years path. throats.....	7	25.92
84 females under 8 years normal throats.....	7	8.33
79 males over 8 years path. throats.....	8	10.12
237 males over 8 years normal throats.....	26	10.97
57 females over 8 years path. throats.....	5	8.75
206 females over 8 years normal throats.....	21	10.19

Further analysis shows that the incidence of positive cultures is higher in females with pathological throats than in females with normal throats (14.28 per cent in the former and 9.65 per cent in the latter). The incidence of positive cultures is higher in children under eight years old with pathological throats than in children under eight years old with normal throats (16 per cent in the former and 8.90 per cent in the latter). The incidence of positive cultures is higher in females under eight years old with pathological throats than in females under eight years old with normal throats (25.92 per cent in the former and 8.33 per cent in the latter).

If on the other hand we compare, in the various groups the incidence of pathological throat conditions in children who have positive cultures with the incidence of pathological throat conditions in children who have negative cultures (Table III) we find:

	Per cent
In 85 children with pos. cultures, 25 path. throats.....	29.41
In 715 children with neg. cultures, 186 path. throats.....	26.01

Further analysis shows that the incidence of pathological throats is higher in females with positive cultures than in females with negative cultures.

The incidence of pathological throats is higher in children under eight years old with positive cultures than it is in children under eight years old with negative cultures.

The incidence of pathological throats is higher in females under eight years old with positive cultures than it is in females under eight years old with negative cultures. From

TABLE III

COMPARING THE INCIDENCE OF PATHOLOGICAL THROATS IN CHILDREN HAVING POSITIVE CULTURES AND THOSE HAVING NEGATIVE CULTURES

	Pathological throats	
	Number	Per cent
85 children with positive cultures.....	25	29.41
715 children with negative cultures.....	186	26.01
45 males with positive cultures.....	13	28.88
381 males with negative cultures.....	114	29.92
40 females with positive cultures.....	12	30.00
334 females with negative cultures.....	72	21.55
25 children under 8 years positive cultures.....	12	48.00
196 children under 8 years negative cultures....	63	32.14
60 children over 8 years positive cultures.....	13	21.66
519 children over 8 years negative cultures.....	123	23.69
11 males under 8 years positive cultures.....	5	45.45
99 males under 8 years negative cultures.....	43	43.43
14 females under 8 years positive cultures.....	7	50.00
97 females under 8 years negative cultures.....	20	20.62
34 males over 8 years positive cultures.....	8	23.53
282 males over 8 years negative cultures.....	71	25.17
26 females over 8 years positive cultures.....	5	19.23
237 females over 8 years negative cultures.....	52	21.94

In the above analysis it appears that in the series of cases under discussion positive cultures were found with about the same frequency in pathological throats as in normal throats, 11.84 per cent as compared with 10.18 per cent, and that pathological throats were found but slightly more frequently in children who had positive cultures than in those with negative cultures, 29.41 per cent as compared with 26.01 per cent. We think it would be unsafe to draw conclusions from differences so slight as the above.

Up to this point in the analysis no attention has been paid to the virulence of the cultures. Of the 85 positive cultures 64 were tested for virulence and 8, or 12.50 per cent, found virulent. Of the eight virulent cultures, three were found in males and five in females. Three occurred in children under eight years of age and five in children over eight years. Five occurred in children with apparently normal throats and three in children with evidently pathological throats.

Beginning May 13, 1912, three months after the first culture, the same 800 children were re-examined. The results have been analyzed and summarized in Table IV.

Examination of Table IV shows that at this time there were 69 positive cultures among the 800 children, 8.62 per cent. The percentage among males and females was again practically the same (8.45 per cent and 8.82 per cent). Children under eight years old gave an incidence of 9.50 per cent, as compared with 8.29 per cent in children over eight years old. Males under eight years old gave 8.18 per cent of

TABLE IV

SECOND EXAMINATION OF 800 CHILDREN, SCHOOL V, MAY, 1912.  
ANALYZED WITH REFERENCE TO AGE, SEX, POSITIVE  
CULTURES AND PATHOLOGICAL THROATS

	Pos. cultures		Path. throats	
	Number	Per cent	Number	Per cent
800 children 4-17 years.....	69	8.62	107	13.37
426 males.....	36	8.45	66	15.49
374 females.....	33	8.82	41	10.96
221 children under 8 years....	21	9.50	35	15.83
579 children over 8 years....	48	8.29	72	12.43
110 males under 8 years.....	9	8.18	19	17.27
111 females under 8 years....	12	10.81	16	14.41
316 males over 8 years.....	27	8.54	47	14.87
263 females over 8 years.....	21	7.98	25	9.50

positive cultures as compared with 10.81 per cent in females under eight years old. Males over eight years old gave 8.54 per cent of positive cultures and females over eight years gave 7.98 per cent of positive cultures. As was the case in the previous examinations, so in this examination the results seem remarkable for their lack of variation between different age and sex groups.

It will be noticed that at the time of the last examination the total incidence of positive cultures was somewhat less than at the first examination and that the number of pathological throats was only about half as great as at the first examination. These results were probably influenced by the seasons at which the two examinations were made, the first occurring in February, the second in May. Notwithstanding the marked reduction in the incidence of pathological throat conditions at the time of the last examination, the relative distribution in the different age and sex groups is almost exactly the same as at the first examination; thus the incidence of pathological throats is higher in males (15.49 per cent) than in females (10.96 per cent), higher in children under eight years old (15.83 per cent) than in children over eight years old (12.43 per cent), and reaches its maximum in males under eight years old (17.27 per cent).

If we compare in the various groups the incidence of positive cultures in pathological throats with the incidence of positive cultures in normal throats (Table V) we find as follows:

	Per cent
In 107 children with path. throats, 15 positive cultures..	14.01
In 693 children with normal throats, 54 positive cultures ...	7.93

The incidence of positive cultures is higher in females with pathological throats, 26.82 per cent, than in females with normal throats, 6.60 per cent. It is higher in children under eight years old with pathological throats, 22.85 per cent, than in children under eight years old with normal throats, 6.98 per cent. It is much higher in females under eight years old

TABLE V

COMPARING THE INCIDENCE OF POSITIVE CULTURES IN CHILDREN  
HAVING PATHOLOGICAL THROATS AND THOSE HAVING  
NORMAL THROATS

	Positive cultures	
	Number	Per cent
107 children with path. throats.....	15	14.01
693 children with normal throats.....	54	7.93
66 males with path. throats.....	4	6.06
360 males with normal throats.....	32	8.88
41 females with path. throats.....	11	26.82
333 females with normal throats.....	22	6.60
35 children under 8 years with path. throats....	8	22.85
186 children under 8 years with normal throats.....	13	6.98
72 children over 8 years with path. throats.....	7	9.86
507 children over 8 years with normal throats.....	41	8.08
19 males under 8 years with path. throats .....	0	0.00
91 males under 8 years with normal throats.....	9	9.89
16 females under 8 years with path. throats.....	8	50.00
95 females under 8 years with normal throats.....	4	4.21
47 males over 8 years with path. throats.....	4	8.51
269 males over 8 years with normal throats.....	23	8.55
25 females over 8 years with path. throats.....	3	12.00
238 females over 8 years with normal throats.....	18	7.56

with pathological throats, 50 per cent, than in females under eight years old with normal throats, 4.21 per cent.

If on the other hand we compare the incidence of the pathological throat conditions occurring in children who have positive cultures with the incidence of pathological throat conditions in children who have negative cultures (Table VI) we find:

Per cent

In 69 children with pos. cultures, 15 with path. throats ...	21.73
In 731 children with neg. cultures, 92 with path. throats..	12.58

As was the case in the analysis of the first examination so in this one there was a higher incidence of pathological throats in the females with positive cultures than in females with negative cultures (33.33 per cent as compared with 8.79 per cent). The incidence of pathological throats was higher in children under eight years of age with positive cultures than in children under eight years with negative cultures (38.09 per cent as compared with 13.50 per cent). The incidence of pathological throats is much higher in females under eight years old with positive cultures than in females under eight years old with negative cultures (66.66 per cent as compared with 8.08 per cent).

Analyzed from the standpoint of the virulent cultures the following results are obtained: Of the 69 positive cultures 41 were tested and three found virulent (7.31 per cent). None

TABLE VI

COMPARING THE INCIDENCE OF PATHOLOGICAL THROATS IN CHILDREN  
HAVING POSITIVE CULTURES AND THOSE HAVING NEGATIVE CULTURES

	Pathological throats	
	Number	Per cent
69 children with positive cultures.....	15	21.73
731 children with negative cultures .....	92	12.58
36 males with positive cultures.....	4	11.11
390 males with negative cultures.....	62	15.89
33 females with positive cultures.....	11	33.33
341 females with negative cultures.....	30	8.79
21 children under 8 years with positive cultures.	8	38.09
200 children under 8 years with negative cultures.	27	13.50
48 children over 8 years with positive cultures..	7	14.58
531 children over 8 years with negative cultures.	65	12.24
9 males under 8 years with positive cultures....	0	00.00
101 males under 8 years with negative cultures.	19	18.81
12 females under 8 years with positive cultures.	8	66.66
99 females under 8 years with negative cultures.	8	8.08
27 males over 8 years with positive cultures....	4	14.81
289 males over 8 years with negative cultures...	43	14.87
21 females over 8 years with positive cultures...	3	14.28
242 females over 8 years with negative cultures.	22	9.09

of the three virulent cultures occurred in throats which were evidently pathological.

As previously stated, 85 positive cultures were found among 800 children at the first examination and three months later a second examination of the same 800 children yielded 69 positive cultures. Comparison of the two lists of positive cultures revealed the striking fact that only 10 of the children gave positive cultures at both examinations. That is to say, 75 of the children who gave positive cultures at the first examination gave negative cultures at the second examination and 59 of the children who gave positive cultures at the second examination gave negative cultures at the time of the first examination. Does this mean that 75 of the children with positive cultures at the time of the first examination had succeeded in getting rid of the diphtheria bacilli which they had been carrying in their throats and that 59 children who gave negative cultures at the time of the first examination subsequently became infested? We think that such conclusions are not justified. We pointed out in our first communication that a single culture from each of a group of individuals will yield a number of positive cultures far below the real incidence of carriers and that two examinations will nearly double the number of positive cultures obtained. We think it safe to assume that many of the 85 children who gave positive cultures at the first examination still carried diphtheria bacilli in their throats at the time of the second examination

and that a majority of the 69 children who gave positive cultures at the second examination probably had diphtheria bacilli at the time of the first examination.\*

The case is somewhat different with regard to the observations of pathological throat conditions, a considerable number of which were acute and were present at one or the other examination but not at both. It seems to us justifiable to combine the positive cultures found on the two examinations and analyze the figures thus obtained, but no such combination is permissible in the case of the observations on pathological throats.

The figures obtained by combining the positive cultures found on the two examinations appear in Table VII.

TABLE VII

RESULTS OF FIRST AND SECOND EXAMINATION OF 800 CHILDREN,  
SCHOOL V, COMBINED AND ANALYZED WITH REFERENCE  
TO AGE, SEX AND POSITIVE CULTURES

	Positive cultures	
	Number	Per cent
800 children 4-17 years.....	144	18.00
426 males.....	75	17.60
374 females.....	69	18.44
221 children under 8 years.....	40	18.09
579 children over 8 years.....	104	17.96
110 males under 8 years.....	17	15.45
111 females under 8 years.....	23	20.72
316 males over 8 years.....	58	18.35
263 females over 8 years.....	46	17.49

Table VII shows that among the 800 children examined there were 144, or 18 per cent, who at one time or another showed a positive throat culture. Males and females showed practically the same percentage of positive cultures (17.60 per cent for males and 18.44 per cent for females). Children under eight years and those over eight years old showed practically the same percentage (18.09 and 17.96 per cent). As was the case in the analysis of the results of the two examinations separately, so in the analysis of the combined results, females under eight years of age showed the highest percentage of positive cultures of any group, 20.72 per cent. Males under eight years old gave 15.45 per cent positive cultures. Males over eight years old, 18.35 per cent, and females over eight years old, 17.49 per cent positive cultures.

Virulence tests were done on the cultures from 99 children and eleven were found virulent, 11.11 per cent. Of the 11 virulent cultures five occurred in males and six in females. Four occurred in children under eight years and seven in children over eight years old. Seven occurred in children with apparently normal throats and four in children with evidently pathological throats.

\* We have a considerable amount of evidence in support of this view which will be presented in a subsequent paper.

As previously mentioned, temperature observations were made on 431 of the children at the time of the last examination.

We wish to analyze the results to see if any relationship can be shown to exist between the temperature, pathological throat conditions and positive cultures.

For this purpose we shall compare the incidence of temperature elevations:

(a) In children with pathological throat conditions and in those whose throats are normal.

(b) In children with positive cultures and those with negative cultures.

(c) In children with positive cultures and pathological throats with those having positive cultures and normal throats.

(d) In children with negative cultures and pathological throat conditions with those having negative cultures and normal throats.

TABLE VIII

	Total	Temp. up to 99°	Temp. over 99°
Pathological throats.....	78	57—73.07%	21—26.92%
Normal throats.....	353	262—74.22%	91—25.77%
Positive cultures.....	39	34—87.17%	5—12.82%
Negative cultures.....	392	285—72.70%	107—27.29%

Table VIII shows the temperature relations between children having pathological throats and those having normal throats and the relation between those having positive cultures and those having negative cultures.

Of the 431 children whose temperature was recorded 78 had pathological throats and 353 had normal throats. The percentage of children whose temperature was above 99° F. was practically equal in the two groups, 26.92 per cent among those with pathological throats and 25.77 per cent among those with normal throats. There were 39 children with positive cultures and 392 with negative cultures. The percentage with an elevation of temperature above 99° F. was higher among the children with negative cultures, 27.29 per cent, than among those with positive cultures, 12.82 per cent.

Table IX shows the relations to temperature elevations of the following four groups:

(1) Positive cultures and pathological throats.

(2) Positive cultures and normal throats.

(3) Negative cultures and pathological throats.

(4) Negative cultures and normal throats.

TABLE IX

		Temp. up to 99°	Temp. over 99°
39 positive cultures	11 path. throats....	8—72.72%	3—27.27%
	28 normal throats...	26—92.85%	2—7.14%
392 negative cultures	67 path. throats....	49—73.13%	18—26.86%
	325 normal throats..	236—72.61%	89—27.38%

The percentage of children with an elevation of temperature above 99° F. is higher among those with positive cultures

and pathological throats, 27.27 per cent, than among those with positive cultures and normal throats, 7.14 per cent, but is about equal to that of children with negative cultures and pathological throats, 26.86 per cent, and of the group with negative cultures and normal throats, 27.38 per cent.

If we regard as carriers those who gave a positive culture at either examination and compare the temperature observations on that group with those who did not give a positive culture at either examination, we find that temperature elevations above 99° occurred with about the same relative frequency in the group who twice gave negative cultures, 25.87 per cent, as in the carrier group, 26.37 per cent.

Table X shows the percentage of temperature elevations in the four groups mentioned above.

TABLE X

	Temp. up to 99°	Temp. over 99°
91 at some time positive cultures	{ 19 path. throats ..   13—68.42% 72 normal throats   54—75.00%   18—25.00%	6—31.58%
340 twice negative cultures	{ 60 path. throats .....   45—75.00% 280 normal throats .....   207—73.92%   73—26.07%	15—25.00%

From this table it appears that temperature elevations above 99° F. occurred slightly more frequently in the group with positive cultures and pathological throats than in the other three groups, temperature elevations in the other three groups occurring with practically the same frequency.

#### SUMMARY, PART I

A single throat culture from each of 800 children attending one of the public schools of Baltimore, in February, 1912, revealed *B. diphtheriae* in 85, 10.62 per cent.

A re-examination of the same 800 children three months later gave 69 positive cultures, 8.62 per cent.

The number of children yielding positive cultures at either one or the other examination was 144, or 18 per cent.

The incidence of positive cultures was practically the same among males and females, and in the different age and sex groups.

At the time of the first examination 211 of the 800 children were noted as having pathological conditions of the throat, 26.37 per cent.

At the time of the second examination (three months later and in milder weather) 107 children were noted as having pathological conditions of the throat, 13.37 per cent.

Pathological throats were more frequent among males than among females, more frequent in children under eight years of age than among children over eight years of age and reached their maximum frequency in males under eight years of age.

At the time of the first examination there were found among the 211 children having pathological throats, 25 positive cultures, 11.84 per cent, and among the 589 children with normal throats, 60 positive cultures, 10.18 per cent.

At the time of the re-examination of the 800 children there were found among the 107 children having pathological throats 15 positive cultures, 14.01 per cent, and among the 693 children with normal throats, 54 positive cultures, 7.93 per cent. At both examinations the highest percentage of positive cultures found in any age and sex group was in females under eight years old having pathological throats. We refrain from drawing any general conclusion from this latter fact owing to the smallness of the group.

At the first examination 25 children were found to have pathological throats among the 85 who gave positive cultures, 29.41 per cent, and 186 children had pathological throats among the 715 who gave negative cultures, 26.01 per cent.

At the second examination 15 children had pathological throats among the 69 who gave positive cultures, 21.73 per cent, and 92 children had pathological throats among the 731 who gave negative cultures, 12.58 per cent. At both examinations the highest incidence of pathological throats found in any age and sex group was in females under eight years having positive cultures. In this case also we refrain from drawing general conclusions from such small numbers.

Virulence tests were done on the cultures from 99 children and 11 were found virulent, 11.11 per cent. It would not be safe to draw conclusions from the distribution of these 11 virulent cultures in the various age and sex groups.

Temperature observations were made on 431 of the children at the time of the last examination. The results have been analyzed to see whether any relationship can be shown to exist between temperature elevations, pathological throat conditions and positive cultures.

Temperature elevations above 99° F. occurred with about the same frequency in the following three groups: (a) Children with pathological throats, (b) those with normal throats and (c) those with negative cultures. They occurred much less frequently among the children with positive cultures.

Analyzed from the standpoint of any influence which the various combinations of cultures and throat condition might have on the temperature it was found that the incidence of temperature elevations was about equal in the following three groups:

- (a) Positive culture and pathological throat.
- (b) Negative culture and pathological throat.
- (c) Negative culture and normal throat.

The incidence of temperature elevations was considerably less in the group with positive cultures and normal throats.

If we regard as carriers those children who gave at either examination a positive culture, we find that the highest incidence of temperature elevations occurring in any group was among carriers who had pathological throat conditions.

#### PART II

1. To determine the persistence of *B. diphtheriae* in the throats of persons having positive cultures but not suffering from clinical diphtheria.

When this investigation was planned we assumed that the persistence of diphtheria bacilli in the throats of carriers could

be determined by selecting a number of individuals having diphtheria bacilli in their throats and making cultures at intervals to determine when they ceased to be carriers. There were evident fallacies in this assumption. In the first place, we had no means of knowing how long diphtheria bacilli had already persisted in the throats of the children selected for this investigation at the time our observations were begun. In the second place, in case a child has a positive culture followed by one or more negative cultures and then another positive culture we cannot exclude the possibility that the bacilli originally present have been gotten rid of and that re-infestation has taken place. It must be conceded that this latter possibility may exist even in the cases in which a positive culture was obtained at every examination; dis-infestation and re-infestation may have taken place in the two weeks interval between the examinations. In the third place, we have a series of observations on a small group of carriers under more carefully controlled conditions which show that daily examinations may be negative over a period of several days followed by positive cultures for a number of consecutive examinations. Care must therefore be exercised in attempting to draw conclusions regarding persistence of the bacilli from the six re-examinations of the 50 children whose cultures were positive at the time of the first examination and who were selected as carriers for further study.

The first column at the extreme left of Table XI contains the serial numbers of the 50 children selected for repeated examinations. The second column contains their serial number in the list of 800 children from which the 50 were selected. The column at the extreme right of the table shows the number of times a positive culture was obtained from each child.

Under each examination are four columns: the first shows whether the culture was positive or negative, the second indicates the virulence or avirulence of the culture isolated, the third gives the temperatures of the children at the time of each examination and the fourth column shows whether a pathological condition of the throat was noted.

+ indicates positive culture.

0 indicates negative culture.

a indicates an *avirulent* culture.

v indicates a *virulent* culture.

P indicates a pathological condition of the throat.

Table XI gives the results of cultures on these 50 children, results of the virulence tests on the bacilli isolated together with the temperature and throat observations. In the six re-examinations (297 cultures) 85 positive cultures were obtained (28.62 per cent). These were distributed as follows:

13 cases	pos. cults.	found on re-exam.	0 times = 0 pos. cults.
16 "	"	"	1 time = 16 "
8 "	"	"	2 times = 16 "
7 "	"	"	3 " = 21 "
0 "	"	"	4 " = 0 "
4 "	"	"	5 " = 20 "
2 "	"	"	6 " = 12 "
<hr/>			
50 cases	297 cultures	85 pos. cults.	(28.62 per cent)

Of the 50 children who had positive cultures at the time of the first examination, only 29 yielded positive cultures two weeks later at the time of the second examination. At the third examination the number of positive cultures had fallen to 15 and at the fourth, fifth, sixth and seventh examinations the number of positive cultures was 11, 12, 12 and 6 respectively.

We think that this progressive decline in the number of positive cultures indicates that the diphtheria bacilli had actually disappeared from the throats of some of the children, but we do not think that the inference can be drawn that all but six of the 50 who at the first examination had positive cultures had gotten rid of their diphtheria bacilli. We have shown previously that the number of positive cultures revealed by two examinations of a group of people will be nearly twice the number revealed by a single examination. More than two examinations would probably still further increase the number of positive cultures found. We may therefore infer that diphtheria bacilli persisted in the throats of considerably more than six of the 50 carriers for a period of six weeks.

### 2. To determine the virulence or non-virulence of the diphtheria bacilli present in the throats of carriers.

Virulence tests were performed on organisms isolated from all except three of the 50 carriers (Nos. 65, 174, 376). Virulent organisms were found in only six of the 47 carriers thus examined (12.76 per cent).

Of the 135 positive cultures obtained from the 50 carriers selected for repeated examination virulence tests were performed on 110; 12, or 10.90 per cent, were found virulent.

### 3. To determine whether the diphtheria bacilli growing in the throats of carriers may undergo a change in virulence; that is, whether a virulent one may become avirulent or an avirulent organism acquire virulence while growing in the throat of a carrier.

Thirty of the carriers in the above series had virulence tests performed on organisms isolated from two or more separate cultures taken at intervals of two weeks or longer, and in only three cases were virulent organisms found at one time and avirulent organisms at another. The results in these three cases were as follows: Case 25 on the first, fourth, fifth, sixth and seventh examination yielded avirulent cultures and on the second and third examination yielded virulent cultures. Case 131 yielded virulent cultures on the first, second and third examination and avirulent cultures on the fourth, fifth and sixth examination. Case 182 yielded virulent cultures on the first and fifth examination and an avirulent culture on the sixth examination. It is, perhaps, needless to say that in these instances in which irregularity occurred in the results of the virulence test on successive cultures, the tests were repeated to check up a possible slip or technical error. In each instance the original results were confirmed.

There are three possible explanations for the above observations:

1. The bacilli may undergo a change during residence in the throat, acquiring or losing virulence.

TABLE XI

2. Virulent and avirulent organisms may be present in the throat at the same time and in isolating them sometimes one and sometimes the other may be obtained.

3. The carrier may lose the organism originally present and re-infestation with another organism of different virulence may take place.

Evidence against the first hypothesis is furnished by the following experiment: Five healthy persons were selected and shown to be free from diphtheria bacilli by daily throat cultures over a period of two weeks. Their throats were then inoculated with a pure culture of avirulent diphtheria bacilli and thereafter daily cultures were taken for a period of weeks, then at intervals of a few days for more than three months, and subsequently at longer intervals for about 15 months. Some of these individuals became carriers as the result of this experiment and their cultures were almost regularly positive for the first few months. Thereafter, in two of the individuals positive cultures were obtained at irregular intervals for as long as 18 months after the beginning of the experiment. From time to time the organisms were isolated in pure culture from the throats of these five persons and tested for virulence. They constantly proved avirulent and at no time did any symptoms develop in the subjects of this experiment referable to the diphtheria bacilli present in their throats.\*

That the second hypothesis, the presence of virulent and avirulent bacilli in the throat of the same person, is improbable is indicated by the fact that in many of the school children who were found to harbor diphtheria bacilli, as many as six isolations were made from a single positive culture and each separate isolation tested for virulence. The results were invariably constant. The organisms were either all virulent or all avirulent, which would have been improbable if virulent and avirulent organisms had been present in the same person.

4. To determine whether any relation exists between the presence of diphtheria bacilli and pathological throat conditions other than clinical diphtheria.

We shall compare first the incidence of pathological throat conditions occurring in children having positive cultures with the incidence of pathological throat conditions occurring in children having negative throat cultures. This comparison is summarized in Table XII which shows in detail the results

TABLE XII

	Pos. cult.	Path. throat	Neg. cult.	Path. throat
2d exam.....	29	17—58.62%	21	12—57.14%
3d exam.....	15	7—46.66%	35	16—45.71%
4th exam.....	11	6—54.54%	39	19—48.72%
5th exam.....	12	8—66.67%	38	15—39.47%
6th exam.....	12	5—41.67%	37	8—21.62%
7th exam.....	6	2—33.33%	42	7—16.66%
	85	45—52.94%	212	77—38.32%

\* A detailed account of this work is to be reported in another paper.

obtained at each re-examination as well as the total results obtained for all of the examinations.

The table shows that for each examination a higher percentage of pathological throat conditions was found in children with positive cultures than in children with negative cultures. The total result for all six examinations shows that 52.94 per cent of the children with positive cultures had pathological throat conditions as compared with 36.32 per cent pathological throat conditions among the children with negative cultures.

If now we compare the incidence of positive cultures in children with pathological throat conditions with the incidence of positive cultures in children having normal throats we get similar results (Table XIII).

TABLE XIII

	Path. throat	Pos. cult.	Norm. throat	Pos. cult.
2d exam.....	29	17—58.62%	21	12—57.14%
3d exam.....	23	7—30.43%	27	8—29.63%
4th exam.....	25	6—24.00%	25	5—20.00%
5th exam.....	23	8—34.78%	27	4—14.81%
6th exam.....	13	5—38.46%	36	7—19.44%
7th exam.....	9	2—22.22%	39	4—10.25%
	122	45—36.88%	175	40—22.85%

At each examination children with pathological throat conditions yielded a higher percentage of positive cultures than did children with normal throats. The totals for the six re-examinations show 36.88 per cent positive cultures occurring in children with pathological throats as compared with 22.85 per cent cultures in children with normal throats.

We are unable to say which is cause and which is effect, although the question seems of some importance. May the presence of diphtheria bacilli in the throat give rise to pathological conditions which do not attain the proportions of those occurring in clinical diphtheria or does the presence of pathological throat conditions favor the lodgment and growth of diphtheria bacilli in the throat? Experience rather points to the latter view since it has been shown that in many instances diphtheria bacilli disappear from the throat after the removal of diseased tonsils. That they persist in some cases after tonsillectomy is to be expected, as their habitat may be lymphadenoid tissue in the nasopharynx other than the tonsils, the nasal passages or the paranasal sinuses.

To gain further light on these questions we have attempted to analyze the relation of positive cultures and pathological throat conditions to elevations of temperature.

The results for the six re-examinations are shown in Table XIV.

The results in Table XIV are not so uniform as those shown in the two preceding tables. At four out of six examinations temperature elevations occurred in a higher percentage of

children with positive cultures than in those with negative cultures and the summary for the six examinations shows temperature elevation in 37.77 per cent of the children with positive cultures as compared with 32.85 per cent of children with negative cultures.

TABLE XIV

	Positive cultures		Negative cultures		Path. throats		Normal throats	
	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.
2d...	29	8—27.58%	21	4—19.05%	29	7—24.18%	21	5—23.81%
3d...	15	10—66.67%	34	13—38.23%	23	10—43.47%	26	13—50.00%
4th...	11	2—18.18%	39	11—28.20%	25	8—32.00%	25	5—20.00%
5th...	12	7—55.33%	38	16—42.10%	23	9—39.13%	27	14—51.55%
6th...	12	4—33.33%	37	12—32.43%	13	4—30.77%	36	12—3—33%
7th...	6	1—16.67%	38	12—31.57%	7	2—28.57%	37	11—29.73%
	55	32—37.77%	207	68—32.85%	120	40—33.33%	172	60—34.88%

With regard to throat conditions the percentage of temperature elevations was practically the same in the group with pathological throats and in those with normal throats, 33.33 per cent and 34.88 per cent respectively.

An attempt has been made to analyze the combined influence of positive cultures and pathological throat conditions on the temperature reaction. The results are seen in Table XV.

TABLE XV

	Pos. cult. and path. throat		Pos. cult. and normal throat		Neg. cult. and path. throat		Neg. cult. and normal throat	
	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.
2d...	17	4	12	4	12	3	9	1
3d...	7	4	8	6	16	6	18	7
4th...	6	2	5	0	19	6	20	5
5th...	8	3	4	4	15	6	23	10
6th...	5	1	7	3	8	3	29	9
7th...	2	1	4	0	5	1	33	11
	45	15—33.33%	40	17—42.50%	75	25—33.33%	132	43—32.57%

It appears that in the series under consideration temperature elevations over 99° F. occurred with about the same frequency in the following three groups: Positive culture and pathological throat, 33.33 per cent; negative culture and pathological throat, 33.33 per cent; and negative culture and normal throat, 32.57 per cent. Temperature elevations occurred somewhat more frequently in the group with positive cultures and normal throats, 42.50 per cent.

##### 5. To determine by history and observation whether:

- (a) Any of the carriers investigated have at any previous time had clinical diphtheria,
- (b) Any of them develop clinical diphtheria during the period they are under observation,
- (c) Any of them has ever been exposed to a case of clinical diphtheria,

(d) Any one in contact with the carriers investigated develops clinical diphtheria.

In the present state of our knowledge the most vital question in regard to diphtheria bacillus carriers seems to be their relation to the community; that is, how serious a menace they constitute.

Having as a result of the present investigation 160 carriers \* under observation we determined to see whether we could confirm the observations reported in our previous communication on this subject. The results are shown in Table XVI.

Summary of answers to the five questions in Table XVI:

1. Had you had diphtheria previous to the time the throat culture was taken?

149 negative replies.

11 affirmative replies.

- 1 No. 163 ..... Diphtheria when a baby
- 1 No. 58 ..... Diphtheria when a small child
- 1 No. 276 ..... Diphtheria 3 years ago
- 1 No. 65 ..... Diphtheria 5 years ago
- 3 Nos. 75, 247, 500 ..... Diphtheria 6 years ago
- 4 Nos. 80, 396, 416, 471 ..... Diphtheria 8 years ago

2. Have you had diphtheria since the culture was taken?

160 negative replies.

3. Had you been exposed to a case of diphtheria before the culture was taken?

146 negative replies.

14 affirmative replies.

- 2 Nos. 599, 787 ..... Exposed 1 year ago
- 1 No. 433 ..... Exposed 2 years ago
- 2 Nos. 31, 693 ..... Exposed 3 years ago
- 3 Nos. 37, 112, 651 ..... Exposed 4 years ago
- 2 Nos. 454, 486 ..... Exposed 5 years ago
- 2 Nos. 126, 522 ..... Exposed 6 years ago
- 1 No. 567 ..... Exposed 8 years ago
- 1 No. 102 ..... Exposed 12 years ago

4. Has any one with whom you have been associated developed diphtheria since the culture was taken?

160 negative replies.

5. Have you had any throat trouble during past year, if so, of what nature?

143 negative replies.

17 affirmative replies.

9 Nos. 61, 344, 345, 362, Sore throat treated at home  
386, 460, 530, 749, 756, without physician

2 Nos. 47, 613 ..... Sore throat treated at home by physician

5 Nos. 164, 326, 383, 500, Sore throat. No note as to  
687 ..... physician

1 No. 483 ..... Sore throat. Tonsillectomy 1912

\* The number of individuals with positive cultures at the first examination of the 800 children was 85, as mentioned in Part I, and from these were selected the 50 carriers for the more intensive study reported in Part II. The second examination of the 800 children revealed 69 carriers, only 10 of whom were positive at the earlier test, giving us 144 individuals positive one time or the other. As the result of additional cultures taken on some of these same 800 children but not included in this report, 16 other carriers were discovered and since they were available, the entire 160 were used for the study of their relation to the community.

These results require little in the way of comment. We realize that one cannot rely implicitly on the accuracy of replies made by school children to such a set of questions as the above, but as much care as possible was exercised in trying to obtain accurate histories and not only were the children questioned but they were visited in their homes by the school nurse, Mrs. H. E. Knorr, who carried out this part of the investigation and questioned the parents and guardians of the children most carefully. Moreover, the children themselves were under observation for a considerable length of time in the school and we could learn of no case of diphtheria developing among them or any of their associates.

#### THE NATURE OF THE DIPHTHERIA BACILLI PRESENT IN THE POSITIVE CULTURES

At this point a few words may be appropriate about the "diphtheria bacilli" present in the "positive cultures." Unless specific statements are made concerning the methods employed for their recognition, questions are apt to arise as to the identity of the organisms present in the throats of these carriers and assumed by us to be Klebs-Loeffler bacilli. Among the questions to be anticipated might be mentioned the following:

Were we dealing with "pseudo-diphtheria bacilli"? *B. xerosis* or *B. hofmanni*? Barred, banded or solid-staining forms? Diphtheroid organisms?

How would they be classified on the Wesbrook-Wilson-McDaniel scale? As A or C<sub>2</sub>? As B<sub>2</sub> or G?

As the result of our experience in 1911, we felt prepared to recognize *B. diphtheriae* as it appears in mixed culture from the throats of carriers. In the present work, accordingly, our original diagnosis was based solely upon the morphology, arrangement and staining characteristics of the organisms seen in films from 18- to 24-hour cultures on Loeffler's blood serum and stained by the Neisser method. To check this original diagnosis an attempt was made to isolate the diphtheria organisms present in the positive cultures. This was carried out and the pure cultures subjected to further examination in 163 instances \* as follows:

1. Staining by Neisser, Loeffler's methylene blue and Gram methods.
2. Observation of cultural characteristics.
3. Tests for virulence.

The results of these tests on pure cultures may be summarized briefly:

1. *Staining and Morphology*.—After growth on Loeffler's serum for 18 to 24 hours the organisms were for the most

\* *B. diphtheriae* was isolated from all except a very few of the positive cultures obtained and referred to in Parts I and II of this paper, but unfortunately many of the strains were lost before their examination was completed. This occurred as the result of transference to a lot of Loeffler's serum which had been insufficiently sterilized; when this was discovered many of our cultures were hopelessly overgrown with *B. subtilis*. Thus, although practically all had been previously examined as to staining and cultural characteristics, only 163 stains were available for the complete study, including the test for virulence.

part long and slender, showing polar granules prevailingly terminal in location and a marked tendency to typical group arrangement in angles and parallels. All would be classified as A, C, or D on the Wesbrook scale, with the long, slender form C greatly preponderating, while types A and D were rarely encountered. With the Neisser stain most satisfactory results were obtained when the methylene blue and Bismarck brown were each allowed to act for from three to five minutes instead of as many seconds in the way usually recommended. With the Gram stain the polar granules retained the stain, the bodies being much less resistant to decolorization by alcohol.

2. *Cultural Characteristics*.—On Loeffler's blood serum the growth was relatively abundant and the colonies round, discrete, opaque, rather putty-like in color and consistence and never causing liquefaction of the medium.

On plain agar the growth was definite but feebler, scantier and the individual colonies tiny.

In litmus milk there was no coagulation but a definite change of color was produced as compared with the slightly alkaline control tubes—the resultant color being a lilac shade indicating a slight change of reaction from alkaline to neutral.

In bouillon a slight surface film was frequently seen, its presence apparently depending to a considerable extent on the method used in inoculating the tube. Slight turbidity might be observed early, but for the most part the medium was clear and a deposit of tiny granules could be seen on the sides and bottom of the tube capable of producing slight but definite turbidity when the tube was shaken.

The tests for the action on sugars were performed with sugar-free broth to which the sugar was added prior to the final sterilization. No test was considered satisfactory unless a good growth was obtained in the broth. The organisms all produced acid but no gas with dextrose, while neither acid nor gas was formed from saccharose.

3. *Virulence Tests*.—A positive result was reported when the animal died within 4 days after injection and showed characteristic lesions at autopsy, while the protected, control, animal survived. In most instances the virulent organisms killed within two days. All surviving animals were kept under observation for weeks after the date of injection. The results of these tests are reported elsewhere in this paper, but it may be mentioned here that many of the cultures were tested on guinea-pigs more than once, some of them many times, and the original result confirmed in each instance.

*Diphtheria-Like Organisms*.—From the throat cultures regarded as negative but containing any organisms resembling even remotely the diphtheria bacillus, isolations were made in like manner. When in pure culture many of them could be ruled out at once on a basis of morphology and staining characteristics or the appearance of the growth on blood serum. Of the remainder, practically all were members of the "diphtheria group" of organisms, resembling rather closely the diphtheria bacillus in their growth on Loeffler's medium, but easily differentiated from it by their size, shape and staining characteristics, despite their rather typical arrangement. This was



TABLE XVI—Continued

Culture number	Remarks						Culture number	Remarks					
	Diphtheria previous to culture	Diphtheria subsequent to culture	Exposure to diphtheria previous to culture	Diphtheria in association with subsequent to culture	Any throat trouble in past year			Diphtheria previous to culture	Diphtheria subsequent to culture	Exposure to diphtheria previous to culture	Diphtheria in association with subsequent to culture	Any throat trouble in past year	
372	No.	No.	No.	No.	No.	Sister had diphtheria 15 years ago, before birth of pupil	535	No.	No.	No.	No.	No.	
376	"	"	"	"	"		556	"	"	"	"	"	
379	"	"	"	"	"		567	"	"	Yes.	"	"	Brother and sister had diphtheria 8 years ago.
382	"	"	"	"	"		576	"	"	No.	"	"	
383	"	"	"	"	"	Yes. Had sore throat during past winter.	578	"	"	"	"	"	
385	"	"	"	"	"	No.	582	"	"	"	"	"	
386	"	"	"	"	"		591	"	"	"	"	"	
396	Yes.	"	"	"	"	Had diphtheria 8 years ago. Antitoxin used. House fumigated.	592	"	"	"	"	"	Case of diphtheria in same house one year ago. House fumigated afterwards.
402	No.	"	"	"	"		599	"	"	Yes.	"	"	
404	"	"	"	"	"		603	"	"	No.	"	"	
409	"	"	"	"	"		613	"	"	"	"	"	Yes. Had severe sore throat July, 1912. Treated by physician. Not confined to bed.
411	"	"	"	"	"		628	"	"	"	"	"	
413	"	"	"	"	"		650	"	"	"	"	"	
414	"	"	"	"	"		651	"	"	Yes.	"	"	Brother had diphtheria 4 years ago. Pupil sent to live elsewhere after diagnosis was made; returned home after house was fumigated.
416	Yes.	"	"	"	"	Had diphtheria 8 years ago. Antitoxin used. House fumigated.	670	"	"	No.	"	"	
419	No.	"	"	"	"		672	"	"	"	"	"	
423	"	"	"	"	"		675	"	"	"	"	"	
433	"	"	Yes.	"	"	Playmate had diphtheria 2 years ago.	678	"	"	"	"	"	
434	"	"	No.	"	"		679	"	"	"	"	"	
446	"	"	"	"	"		684	"	"	"	"	"	
449	"	"	"	"	"		687	"	"	"	"	"	
450	"	"	"	"	"	Brother had diphtheria 5 years ago. Antitoxin used. House fumigated. Had sore throat during past winter. Treated at home without physician.	691	"	"	"	"	"	
454	"	"	Yes.	"	"		693	"	"	Yes.	"	"	Had several mild attacks of sore throat during past winter. Enlarged tonsils.
460	"	"	No.	"	Yes.		702	"	"	No.	"	"	
463	"	"	"	"	No.		705	"	"	"	"	"	Brother had diphtheria 3 years ago. Antitoxin used and flat fumigated.
467	"	"	"	"	"		717	"	"	"	"	"	
469	"	"	"	"	"		718	"	"	"	"	"	
471	Yes.	"	"	"	"	Had diphtheria 8 years ago. Antitoxin used. House fumigated.	730	"	"	"	"	"	
481	No.	"	"	"	"		732	"	"	"	"	"	
482	"	"	"	"	"		733	"	"	"	"	"	
483	"	"	"	"	Yes.	Repeated mild attacks of sore throat. Tonsils removed April, 1912.	736	"	"	"	"	"	
486	"	"	Yes.	"	No.	Brother had diphtheria 5 years ago.	749	"	"	"	"	"	
490	"	"	No.	"	"		756	"	"	"	"	"	
493	"	"	"	"	"		760	"	"	"	"	"	
496	"	"	"	"	"		783	"	"	"	"	"	
500	Yes.	"	"	"	Yes.	Had diphtheria 6 years ago. Had severe sore throat during past winter. Enlarged tonsils.	787	"	"	Yes.	"	"	Had sore throat during past winter. Treated at home without physician. Had severe sore throat during past winter. Treated at home without physician.
522	No.	"	Yes.	"	No.	Brother had diphtheria 6 years ago. Antitoxin used. House fumigated.	796	"	"	No.	"	"	
530	"	"	No.	"	Yes.	Had sore throat during past winter. Not severe. Treated at home without physician. Enlarged tonsils.							Playmate living in same house had diphtheria one year ago.
531	"	"	"	"	No.								
534	"	"	"	"	"								

confirmed when tested on litmus milk and sugars, as these organisms reacted quite differently from *B. diphtheriae*, producing no acid with either dextrose or saccharose but definite increase in alkalinity with litmus milk. These organisms could be classified, therefore, as *B. hofmanni*. The xerosis bacillus which produces acid with both dextrose and saccharose was very rarely encountered, probably because we were dealing with cultures from the throat rather than the nose.

All of these organisms of the "diphtheria group" isolated from throat cultures regarded by us as negative were also tested for virulence, the number of strains thus tested being quite as large as that of true diphtheria bacilli. No virulent strain was encountered and they seemed to be uniformly without pathogenicity.

As a result of this study of the organisms isolated from the throat cultures we concluded that:

1. The original diagnosis of cultures positive or negative for *B. diphtheriae* was confirmed.
2. The "avirulent diphtheria bacilli" of which we speak are indistinguishable from true, virulent *B. diphtheriae* except by the animal test of toxin production.
3. The other members of the diphtheria group of organisms encountered in cultures from the throat need cause very little difficulty in recognition and are of no pathogenic importance.

#### SUMMARY, PART II

It should be borne in mind that whereas Part I of this paper deals with the results of examination of 800 school children, some of whom were found to be diphtheria bacillus carriers, Part II concerns the further study of 50 of these same children, all of whom were shown to be carriers at the time the investigation was begun. Consequently, since certain of the conditions were so different in the two groups studied and 50 of the children appear in both groups, not all of the results reported in the first portion can be directly compared with those in the second. Thus, in Part I the percentage incidence of bacillus carriers is emphasized, while in Part II which is concerned only with carriers, it is the persistence of the bacilli—the duration of the carrier state—which receives attention. In the following summary of the findings in Part II, therefore, only such portions of the results recorded in Part I as have a definite bearing on the subject in hand, will be included for comparison; these are placed in brackets.

#### *1. How long may diphtheria bacilli persist in the throats of persons having positive cultures but not suffering from clinical diphtheria?*

Fifty children who had positive cultures at the time of the first examination were re-examined at intervals of two weeks over a period of three months. The total number of cultures made on the six re-examinations was 297, of these 85, or 28.62 per cent, were positive. At the time of the last examination diphtheria bacilli were found in only six of the 50 children.

#### *2. What is the virulence of the diphtheria bacilli present in the throats of carriers?*

Cultures from 47 of the children in the above series were tested for virulence and six found virulent, 12.76 per cent.

Of the 135 positive cultures obtained from the 50 children selected for repeated examination, virulence tests were performed on 110; 12, or 10.90 per cent, were found virulent.

(In Part I we reported (1) that of the 85 positive cultures encountered in the first examination of the 800 children, 64 were tested by guinea-pig inoculation and eight, or 12.50 per cent, found virulent; (2) that on the second examination 41 of the 69 positive cultures were tested and 3, or 7.31 per cent, found virulent; (3) that in all, cultures from 99 different children were tested and 11, or 11.11 per cent, were virulent.)

#### *3. Do diphtheria bacilli growing in the throats of carriers undergo a change in virulence?*

In the case of three of the carriers in this series sometimes virulent organisms and sometimes avirulent organisms were found. This fact does not constitute proof that avirulent organisms acquired virulence or that virulent organisms became avirulent.

#### *4. Does any relation exist between the presence of diphtheria bacilli and pathological throat conditions other than clinical diphtheria?*

Pathological throat conditions were found more frequently in children who had positive cultures than in those with negative cultures, 52.94 per cent in the former and 36.32 per cent in the latter.

(In the first examination of the 800 children reported in Part I, pathological throat conditions were found in 29.41 per cent of those with positive cultures and in 26.01 per cent of those with negative cultures. At the second examination, the difference was more striking, 21.73 per cent and 12.58 per cent.)

A higher percentage of positive cultures was found in children with pathological throats than in those with normal throats, 36.88 per cent in the former and 22.85 per cent in the latter.

(The same holds true for Part I; at the first examination 11.84 per cent of positive cultures were found in the children with pathological throats and 10.18 per cent in those with normal throats. At the second examination the difference was more pronounced, 14.01 per cent and 7.93 per cent.)

Temperature elevations occurred slightly more frequently among children giving positive cultures than among those giving negative cultures.

(The exact reverse of this was found in the study of the 800 children reported in Part I.)

Temperature elevations occurred with about equal frequency among children having pathological throats and among those with normal throats.

(This is in agreement with the findings with the other group of children.)

Studying the combined influence of culture and throat condition on the temperatures, we found that the highest percentage of temperature elevations occurred in the group with positive cultures and normal throats.

(To quote from Part I, "It was found that the incidence of temperature elevations was about equal in the following three groups:

- (a) Positive culture and pathological throat.
- (b) Negative culture and pathological throat.
- (c) Negative culture and normal throat.

The incidence of temperature elevations was considerably less in the group with positive cultures and normal throats."

We do not pretend to reconcile this statement with the findings in Part II indicated above, nor is the matter simplified by a further quotation from Part I as follows: "If we regard as carriers those children who gave at either examination a positive culture, we find the highest incidence of temperature elevations occurring in any group was among carriers who had pathological throat conditions."

Our general impression upon this point is that the mere presence of diphtheria bacilli in the throats of carriers is not responsible for any objective pathological condition whatever, and does not cause an elevation of temperature. On the other hand, persons with pathological throat conditions other than clinical diphtheria, particularly those with diseased tonsils, seem to furnish a somewhat more favorable field for the lodgment and growth of the diphtheria bacillus than that afforded by persons with normal throats.

*5. What is the previous and subsequent history and the relation to the community with reference to clinical diphtheria of persons having positive cultures?*

An investigation of 160 diphtheria bacillus carriers to determine these points yielded the following results:

(a) Only 11 of the 160 carriers gave a history of having had diphtheria, but none more recently than three years previous to the time throat cultures were taken.

(b) None of the 160 carriers subsequently developed diphtheria during the period that they were under observation.

(c) Fourteen of the 160 carriers gave a history of exposure to diphtheria at a period varying from 1 to 12 years previous to the time cultures were made.

(d) A painstaking investigation revealed no case of diphtheria developing among any of the associates of the 160 carriers.

*6. What is the nature of the diphtheria bacilli present in the positive cultures?*

This has been covered in the section devoted to this subject, but our conclusions may be repeated here. The diphtheria bacilli found in the throats of these carriers were in all respects typical Klebs-Loeffler organisms. The non-virulent diphtheria bacilli apparently differ from the virulent bacilli only in their ability to produce toxin. Since the other members of the diphtheria group encountered in the throat are readily distinguished from *B. diphtheriae*, they need cause very little difficulty in diagnosis. They are of no pathogenic importance.

#### CONCLUSIONS

We have preferred not to draw a large number of conclusions from these investigations, thinking it wiser merely to state the results obtained. With regard to a few points, how-

ever, owing to their importance, we wish to express our conviction.

First: The diphtheria bacilli present in a majority of healthy carriers \* are avirulent.

Second: Avirulent bacilli cannot produce diphtheria.

Third: We have no proof that avirulent diphtheria bacilli can acquire virulence.

For the above reasons we conclude that the carriers of avirulent diphtheria bacilli do not constitute a menace to any one in particular or the community as a whole and that any interference with their liberties on the grounds of their being carriers is unwarranted and not justifiable.

This stand, of course, immediately raises the question as to what constitutes a valid test of virulence. We believe that the standard guinea-pig test may be taken as a safe index of the virulence or non-virulence of diphtheria bacilli for human beings. We have a certain amount of evidence in support of this belief to be presented in a subsequent paper. It may be justifiable, and under certain conditions advisable, to isolate carriers until the virulence of the organism present can be determined, but if the culture proves avirulent for the guinea-pig, further detention of the carrier does not seem justifiable.

We realize fully the time and expense entailed in applying the guinea-pig test, but think this does not equal the inconvenience to the individual and economic loss incurred by needless isolation of a carrier of avirulent bacilli.

There is urgent need of a simpler, quicker and less expensive virulence test.

Fourth: The carrier of virulent diphtheria bacilli occupies quite a different position from that of the carrier of avirulent bacilli. While we think that the danger from the former has perhaps been overestimated we recognize the fact that diphtheria bacilli derived from him may give rise to the disease in susceptible persons. In this connection we have pointed out in a previous communication the need of a satisfactory and efficient means of ridding carriers of virulent diphtheria bacilli.

\* The term "healthy" carrier is used in distinction to "convalescent" or "contact" carrier.

#### ERRATUM

Attention is called to a typographical error on page 364 of the October BULLETIN, in the article entitled "The Coagulation Time of Citrated Plasma on Recalcination," by H. C. Gram. The fourth paragraph, second column, should read as follows:

"About 4.5 c. cm. of blood are taken with a curved needle into a centrifuge tube divided into tenths of a c. cm. and containing .5 c. cm. of 10 per cent sodium citrate solution. After standing for about an hour the corpuscles will have sedimented—excepting in cases of polycythaemia—so as to allow one to draw off .1 c. cm. of plasma for each of the four miniature test-tubes which have previously been inserted into the holes in the cork of the Dewar flask."

# THE TREATMENT OF NEUROSYPHILIS BY THE INTRASPINAL ROUTE

WITH THE REPORT OF A CLINICAL STUDY OF A SERIES OF CASES TREATED FROM THE POINT OF VIEW OF INCREASED PERMEABILITY OF THE MENINGES

By ALBERT KEIDEL and JOSEPH EARLE MOORE

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Since the introduction by Swift and Ellis<sup>1</sup> of a practical method for the intraspinal treatment of neurosyphilis, testimony has been forthcoming from many sources in favor of its efficacy in cases which stubbornly refuse to yield to ordinary methods of treatment. That this endorsement is not unanimous, however, is seen in the objections raised by some authors, notably Sachs and Dercum.

Sachs<sup>2</sup> objects to intraspinal medication on the grounds that it is of no more clinical or serological value than the routine administration of arsphenamine intravenously combined with mercury in some form. Dercum,<sup>3</sup> in a recent review of the subject, condemns intraspinal therapy as unscientific and claims that any benefit derived from it is wholly due to the incidental spinal drainage, from which by itself he has obtained brilliant results in the treatment of neurosyphilis.

In the main these objections have been outweighed by the work of others, but until the mechanism by which this form of treatment becomes effective is understood, uncertainty will undoubtedly continue to render the choice of a method of treatment difficult.

In 1915 Swift<sup>4</sup> outlined the various methods available for the intraspinal treatment of syphilis and summarized the theories and the known facts regarding the mode of action of arsphenaminized serum. His conclusions are worth reviewing: (1) such serum is spirochæticidal<sup>5</sup>; (2) it may contain syphilitic antibodies; (3) the normal human serum may contain substances which when brought into contact with the syphilitic exudate cause it to resolve; (4) the acute irritation produced by the serum may exert a beneficial effect on the chronic inflammatory process; and (5) the local irritation may increase the permeability of the meninges. Of these conclusions the first and third are based on experiment, while the remaining ones are inferences which, while not lacking in some experimental support, have nevertheless not as yet been proved. The fifth conclusion, that of the hypothetical increase in the permeability of the meninges, has seemed to us to be susceptible of clinical investigation by observing the

extent to which this factor enters into the beneficial results of intraspinal medication. Our paper deals with this phase of the subject.

Permeability of the meninges, or more strictly speaking, of the choroid plexuses and the meninges, in the normal individual appears to be limited almost exclusively to the production and elimination of cerebrospinal fluid. Under normal conditions substances in the blood stream, including bacteria, immune bodies, and most drugs are excluded from the cerebrospinal fluid circulation. In this sense the choroid-plexus-meningeal complex constitutes a valuable defense mechanism for the central nervous system, as illustrated for example in chronic mercurial poisoning<sup>6,7</sup> and septicemias.<sup>8</sup>

Under pathological conditions involving these structures (choroid plexus and meninges) however, their impermeability appears to be affected, and bacteria and blood elements pass into the central nervous system.<sup>9,10</sup> Contrary to what might be expected under this condition other substances in the blood-stream, notably drugs and possibly immune bodies, continue to be largely excluded, although there appear to be exceptions to this, as will be explained later. At any rate it may be definitely stated that failure of routine antisyphilitic treatment in neurosyphilis depends upon this difficulty for mercury and arsphenamine to pass the barrier set up by the choroid-plexus-meningeal complex in sufficient amounts to make the concentration spirochæticidal. It is assumed, however, that the pathological process has modified the defense mechanism sufficiently to permit variable quantities to pass over which may be greater than under normal conditions, and that exceptionally the amount passed might be great enough to reach the desired concentration.

Various observers, among them Benedict,<sup>11</sup> Sicard and Bloch,<sup>12</sup> and Kopke<sup>13</sup> have invariably succeeded in demon-

<sup>1</sup> Rotky: Ztschr. f. Klin. Med., 1912, LXXV, 494.

<sup>2</sup> Sicard, A.: Thèse de Paris, 1899.

<sup>3</sup> This refers to the low incidence of meningitis in septicemias generally.

<sup>4</sup> Mattauschek and Pilez (Ztschr. f. d. ges. Neur. u. Psych., 1910-11, IV, Orig., 697; 1913, XV, 608) have shown in a survey of over 4000 syphilitics, followed over a long period of time, that about 25 per cent of the untreated or badly treated cases will develop clinical neurosyphilis.

<sup>5</sup> Many workers have demonstrated by laboratory tests abnormalities of the cerebrospinal fluid in from 25 to 35 per cent of untreated cases of secondary syphilis (period of generalization).

<sup>6</sup> Benedict (cited by Sachs): Am. J. M. Sc., 1914, CXLVIII, 693.

<sup>7</sup> Kopke and Sicard and Bloch (cited by Mestrebat, W.): Paris, 1912, Footnote 3, p. 93.

<sup>1</sup> Swift, H. F., and Ellis, A. W. M.: New York Med. Jour., 1912, XXVI, 53.

<sup>2</sup> Sachs, B.: Arch. Neurol. and Psychiat., 1919 (March), I, 277.

<sup>3</sup> Dercum, F. X.: Arch. Neurol. and Psychiat., 1920 (March), III, 230.

<sup>4</sup> Swift, H. F.: J. A. M. A., 1915 (July 17), LXV, 209.

<sup>5</sup> Swift, H. F., and Ellis, A. W. M.: Journal Exp. Med., 1913, XVIII, 435; and Swift, H. F.: Jour. Exp. Med., 1916, XXXIV, 373.

ing appreciable quantities of arsenic in the fluid after intravenous administration of arsphenamine in neurosyphilis. Hall and his associates<sup>13</sup> found arsenic after intravenous administration in only 25 to 35 per cent of the cases; Reiger and Solomon<sup>14</sup> in about the same percentage; Mehrrens and MacArthur<sup>15</sup> in 43 per cent of the cases. In all instances the amount is small.

In this connection the work of Flexner and Amoss with poliomyelitis is of interest. They showed<sup>16</sup> that in human cases infected with poliomyelitis, no neutralizing substances (immune bodies) could be demonstrated in the spinal fluid, either early or late in the disease; but that in monkeys immune bodies could be made to appear in the fluid after intravenous injections of immune serum, by first setting up an aseptic meningitis<sup>17</sup> with the intraspinal injection of sterile horse serum. The defense mechanism of the choroid-plexus-meningeal complex was further demonstrated<sup>18</sup> by the following means: a simple intravenous injection of 50 c.c. of a 5 per cent suspension of active spinal cord and medulla (poliomyelitis virus) was unsuccessful in reproducing the disease. If aseptic fluids, such as normal monkey or horse serum, isotonic salt solution, and Ringer's or Locke's solution, or even spinal fluid from another monkey, were first injected intraspinally, an intravenous injection of equal or smaller amounts of virus did promote infection. This seemed to demonstrate, at least for monkeys, an exceedingly delicate defense mechanism, which even very slight irritation was capable of altering in such a way that the passage of virus or immune bodies from the blood to the spinal fluid and tissues of the central nervous system was permitted.

<sup>13</sup> Hall, G. W., Callender, R. J., and Holmlund, E. C.: Arch. Neurol. and Psychiat., 1920, III, 631.

<sup>14</sup> Reiger, J. B., and Solomon, H. C.: J. A. M. A., 1918 (July 6), LXXI, 15.

<sup>15</sup> Mehrrens, H. G., and MacArthur, C. G.: Arch. Neurol. and Psychiat., 1919, II, 369.

<sup>16</sup> Flexner, S., and Amoss, H. L.: Jour. Exp. Med., 1917, XXV, 499.

<sup>17</sup> The existence of an aseptic meningitis after intraspinal injections of sera, originally assumed to exist because of the meningeal symptoms of the reaction, has been proved by Weed, Wegeforth, Ayer, and Felton (see note 26) and by Hall, Callender and Holmlund.

The former found that in cats the intraspinal injection of normal cat serum provoked a cellular reaction which reached its maximum in about 6 hours, after which a sharp decrease occurred in the number of cells for about 48 hours, with a slow return to normal in 120 hours. The extent to which this reaction can reach is shown by Hall and his associates, working with human subjects. They administered autologous serum intraspinally to 18 cases, upon whom they performed repeated spinal punctures at intervals of from one hour to 113 hours after treatment. Two of the cases reacted with a cell count of over 4000, in 11 of the 18 the count rose to over 1000, and in the others nearly as high. They found the time relations essentially as given by Weed, except that the reaction was somewhat more sustained, and the counts had not subsided to normal within 113 hours.

<sup>18</sup> Flexner, S., and Amoss, H. L., Jour. Exp. Med., 1917, XXV, 525.

#### THE APPLICABILITY OF MENINGEAL PERMEABILITY TO NEURO-SYPHILIS. CLINICAL METHOD OF INVESTIGATION AND RESULTS

If such a mechanism could be demonstrated for poliomyelitis it seemed reasonable to assume that it might also be made to apply to the treatment of neurosyphilis. Perhaps the permeability of the meningeal-choroid-plexus complex might be sufficiently altered by irritation to permit the passage from the blood to the nervous system of larger quantities of spirochaeticid drugs than would otherwise pass over, and possibly also of syphilitic antibodies. If such a result could be demonstrated, either clinically or experimentally, might there not lie herein an explanation of a large part of the benefit derived from the Swift-Ellis treatment and its modifications? Stillman and Swift<sup>19</sup> considered this, among other factors, and showed that irritation of the cat's meninges by various substances did not increase the amount of arsenic in the nervous tissues over that present after simple intravenous injections.

However, this still did not exclude the possibility that, in the neurosyphilitic, intraspinal injections might produce an alteration of permeability to drugs or antibodies. We therefore conceived the idea of a clinical investigation which might demonstrate the efficiency of this procedure in the treatment of neurosyphilis. The method we adopted was briefly as follows: an intraspinal injection of mercurialized serum (Byrnes)<sup>20</sup> was given and followed within 24 hours by an intravenous injection of arsphenamine. Mercurialized serum was chosen because its irritating effect, judging from reactions, was much more severe than that of normal autologous or homologous serum, or of serum arsphenamized *in vivo* or reinforced *in vitro*. The dosage was never more than 0.6 mgm. of mercury, often less, as in our experience this amount was sufficient to produce marked signs of irritation, sometimes lasting a week or ten days; and larger doses, as originally recommended by Byrnes (1.2 to 2.4 mgm.), produced such severe reactions as to interfere with the repetition of treatment. The intraspinal injection was given before the intravenous, so that the highest possible concentration of arsenic might be in the blood stream while the irritation was at its height (from 6 to 24 hours after the intraspinal treatment). In this way a maximum amount of the drug might be expected to enter the nervous tissues. Intraspinal treatments were given in courses, usually of six treatments administered one each week, and each course was followed by 10 to 12 weeks of mercury by inunction. No general mercury treatment was given during the course of intraspinal and intravenous injections.

Certainly, if benefit was to be derived from the (theoretical) increase of permeability of the meninges, it should have been attained by this method, which provided a maximum concentration of arsenic in the blood stream at the time of maximum irritation. In addition there were of course two added factors: the hyperemia of the central nervous sys-

<sup>19</sup> Stillman, E., and Swift, H. F., Jour. Exp. Med., 1915, XXII, 286.

<sup>20</sup> Byrnes, C. M.: J. A. M. A., 1914 (Dec. 19), LXIII, 2182.

TABLE I  
Treatment given by us Blood Wassermann Cerebrospinal fluid at start of treatment Cerebrospinal fluid at end of treatment

tem, lasting over a period of several days, and the action of mercurialized serum directly. The effects of the former could hardly be evaluated, while the latter was too limited for comparative estimation, owing to the small doses employed.

Our studies are confined to clinical results alone. We have not made determinations of the arsenic content of the spinal fluid. Twenty-five cases were treated. All those cases which might have been expected to improve under routine intravenous treatment alone were excluded. In most instances, such treatment had been thoroughly employed without success.

In Table I are presented the serological and clinical results of the cases treated by this method. The cases are, mainly for the purpose of convenience, classed roughly under the main heads of general paralysis, tabes dorsalis, cerebrospinal syphilis, and asymptomatic neurosyphilis, manifested by laboratory findings alone. This classification is in some instances arbitrary, since we realize the extreme difficulty of making a positive diagnosis of general paresis, on the one hand, or of excluding it absolutely on the other. It will be noted that

TABLE II

Diagnosis	No. of cases	Clinical result		Serological result	
		Good	Bad	Good	Bad
Tabes dorsalis.....	6	4	2	1	4*
General paresis.....	6	2	4	1	5
Tabo-paresis.....	2	..	2	..	2
Cerebrospinal syphilis.....	8	8	..	15	13
Asymptomatic neurosyphilis.....	3	1	2	..	3
Total.....	25	15	10	17	27

\*One case, with negative serology at the start of treatment, remained unchanged.

classification is in no instance made on the basis of a so-called paretic gold curve. While we feel that in clinical general paresis this type of gold curve is constant, we cannot subscribe to the view of many clinicians that, given such a curve in the absence of clinical signs, the patient has general paresis, nor are we willing to admit that such a patient will develop general paresis. It is not uncommon to find a paretic gold curve in other forms of cerebrospinal syphilis.

In Table II the results are summarized. Generally speaking, clinical results have been good in about 60 per cent of the cases, but serological results have been poor in practically all groups treated. Much to our surprise the poorest results have been obtained in the group of asymptomatic neurosyphilis, the very class which one might expect to help most easily.

#### COMPARISON OF OUR RESULTS WITH THOSE OF THE SWIFT-ELLIS METHOD AND ITS MODIFICATIONS

Comparison of these results with those of other workers leads to the conclusion that the method adopted is unsuccessful. Swift<sup>21</sup> reports 37 cases of neurosyphilis, all but 3

tabetics, treated by his own method or by Ogilvie's modification.<sup>22</sup> In 30 of the cases, or 81 per cent, the Wassermann reaction in the cerebrospinal fluid became negative with 1 c.c.; only 2 later relapsed. Nineteen of these cases were also negative with 2 c.c. Of 18 cases which were negative with 1 c.c. or more of fluid, and had been followed from 10 months to 3½ years without treatment, 14 were still negative with 2 c.c.; 2 were negative with 1 c.c. but positive with 2 c.c.; and only 2 had relapsed to positive with 1 c.c. or less. Walker and Haller<sup>23</sup> report practically uniform clinical improvement in 75 cases of neurosyphilis (48 tabes dorsalis, 6 general paresis, 16 cerebrospinal syphilis, and 5 syphilitic meningitis), treated either by the Swift-Ellis method or with salvarsanized serum intraspinally alone. Serological improvement was also noted in practically all cases, but treatment was usually not carried on long enough to effect a serological cure. References of this sort could be multiplied at length.

An incidental comparison of the results of mercurialized and arsphenaminized serum was inevitable from our work. As far as we know such data are largely lacking from the literature. Haller<sup>24</sup> treated two groups of patients with a small number of doses of each with and without intravenous arsphenamine. The amount of treatment given was, in our opinion, too small adequately to judge the permanent effects; but Haller concluded that the average effect on the laboratory findings in the spinal fluid is greater from one dose of mercurialized serum than from one dose of arsphenaminized serum. The clinical improvement seems to have been approximately parallel, but the best results were obtained in active syphilis of the meninges. Inspection of our results suffices to show that the results obtained from mercurialized serum, used by the method we have described, are inferior to results obtained either by ourselves or by others from the Swift-Ellis method.

#### DISCUSSION

Since our study was begun additional pertinent evidence has accumulated in the literature, and the question of the permeability of the meninges and choroid plexus has been further investigated experimentally. Austrian<sup>25</sup> attempted to produce an experimental meningococcus meningitis in rabbits by intravenous inoculation of the organism, without success. He then repeated the experiment of Flexner and Amoss in an attempt to produce invasion of the cerebrospinal structures from the blood-stream by means of irritation of the meninges. To 20 rabbits, intraspinal injections of 0.5 to 1 c.c. of normal rabbit serum were given, followed in from 30 to 50 minutes by an injection of a standard suspension of meningococcus into an ear vein. Three of these animals developed a typical fatal meningitis, and from the meninges of two others killed one hour after the intravenous injection

<sup>21</sup> Ogilvie, H. S.: J. A. M. A., 1914 (Nov. 28), LXIII, 1936.

<sup>22</sup> Walker, I. C., and Haller, D. A.: Arch. Int. Med., 1916, XVIII, 376.

<sup>23</sup> Haller, D. A.: Arch. Int. Med., 1917, XIX, 997.

<sup>24</sup> Austrian, C. R.: Johns Hopkins Hosp. Bull., 1918, XXIX, 183.

meningococci were found in smears. The remaining fifteen rabbits were negative. This demonstrated that the defense mechanism of the meninges of rabbits, while lowered to some extent against the meningococcus, was not so easily disturbed as that of monkeys against the virus of poliomyelitis.

That in other animals and against other organisms a similar phenomenon exists, and that more difficulties are encountered than in the case of poliomyelitis, was shown recently by Weed, Wegeforth, Ayer and Felton.<sup>26</sup> Working with cats, they had great difficulty in finding an organism which was virulent for the cat's meninges but finally discovered one in *B. lactis aerogenes*. When they injected this organism intravenously a meningitis could not be produced unless overwhelming doses were employed, but after certain procedures that modified cerebrospinal conditions they were able to set up an aerogenes meningitis from small intravenous inoculations. In every instance they succeeded in producing this meningitis by spinal drainage, the puncture being made either a few minutes before or within 30 minutes after the intravenous inoculation of a small dose of the organisms.

They assumed this uniformly successful result to be due to the slowing of the blood-stream within the cranium and the consequent cerebral hyperemia. To quote: "A fairly efficient mechanism of adjustment seems to exist within the cranial cavity. Removal of a certain amount of cerebrospinal fluid is followed by a period of low intracerebral pressure, apparently due to the fact that the compensation for the loss of this fluid, while adequate, is not immediate. But certain vascular adjustments occurring quickly upon withdrawal of the cerebrospinal fluid necessarily fill a large part of the space occupied by the evacuated fluid. The chief vascular alteration seems to be more or less extensive venous engorgement with associated slowing of the blood-stream sufficient to account for at least a portion of the space of the fluid withdrawn."

To meet the objection that meningeal infection might be the result of inoculation of the spinal fluid through the medium of the puncture wound, they attempted to reach the same end—venous stasis and cerebral hyperemia—by alternate methods, as follows: (1) Compression of the jugulars for two minutes immediately after the intravenous injection of organisms; (2) stoppage of the heart for two minutes, followed by resuscitation; (3) intravenous injection of 3 c.c. of 30 per cent saline solution immediately preceding the injection of organisms<sup>27</sup>; and (4) an attempt to increase the permeability of the meninges by intraspinal injections of autologous, homologous, or heterologous sera. The first three methods were followed by a typical meningitis in about 50 per cent of the cases. The results were not as uniform as those following spinal puncture, but were still positive enough to refute the objection of the needle puncture as the source of intrathecal infection and to confirm the opinion that the

factor producing a meningitis was the cerebral hyperemia and the venous slowing. The results of the attempts to produce infection after meningeal irritation are of particular interest. Thirty-nine cats were injected intraspinally with sera as described, and from four hours to five days later (the interval being prolonged in order to permit the effects of the accompanying spinal puncture to disappear) an intravenous inoculation of *B. lactis aerogenes* was made. Only six of the animals, about 15 per cent, developed a fatal meningitis. In the other 33 the reaction was in all respects similar to that in control animals who had received only the intraspinal injections.

It is of considerable interest to note that in the meningitis produced by Weed and his co-workers, no matter which of the five methods enumerated was used, the first evidences of infection in sacrificed animals, or those which died early in the disease, were localized over the cerebral cortex with later rapid spread thence. This appeared long before any signs of infection in the ventricles—evidence that the passage of organisms was not by way of the choroid plexus, but probably by way of the pericapillary spaces.

In a recent paper Amoss and Eberson<sup>28</sup> record their failure to produce meningococcus meningitis in monkeys by the method of intravenous injection of the organisms followed by spinal drainage or the production of an aseptic meningitis. Repeating Austrian's work with rabbits they were similarly unsuccessful, but state that in one of two rabbits deliberate injury to the spinal marrow with the puncture needle was followed by a spread of the infection to the spinal system.

In immunized monkeys, however, agglutinins of meningococcus and para-meningococcus will make their appearance in the spinal fluid following the setting up of a meningitis which may be either aseptic or produced by intraspinal inoculation of the specific organisms. This phenomenon was observed to bear a quantitative relationship to the degree of irritation induced in the meninges.<sup>29</sup>

The same authors, replying to the objection of Herrick<sup>30</sup> that intraspinal injections of antimeningococcus serum in early meningococcemia in man might promote the passing over of organisms from the blood to the cerebrospinal fluid, state that, while this is true for the meningeal irritation produced by other means in poliomyelitis, it is distinctly inhibited when specific immune serum is employed.

This suggests the possibility of a selective meningeal activity hitherto unmentioned which may have to be considered as a factor not only in the Swift-Ellis method for the treatment of neurosyphilis, but more especially in methods which depend for their success on the (theoretic) permeability of the meninges.

The apparent inconsistencies in these experimental results make correlation of the data difficult, if not indeed impossible. We must assume that there exist variations in the integrity and resistance of the meningeal defense mechanism of differ-

<sup>26</sup> Weed, L. H., Wegeforth, P., Ayer, J. B., and Felton, L. D.: Monographs of Rockefeller Institute for Med. Research, No. 12, March 25, 1920, 57.

<sup>27</sup> Weed, L. H., and McKibben, P. S.: Am. J. Physiol., 1919, XLVIII, 512.

<sup>28</sup> Amoss, H. L., and Eberson, F.: Jour. Exp. Med., 1919, XXIX, 605.

<sup>29</sup> Loc. cit., 597.

<sup>30</sup> Herrick, W. W.: Arch. Int. Med., 1918, XXI, 541.

ent animal species, and that this mechanism in a given species exhibits variable degrees of susceptibility to organisms and other substances under the same conditions. For example, the virus of poliomyelitis can easily be transferred from blood-stream to spinal fluid in monkeys by spinal irritation, but in rabbits and cats the *Meningococcus* and *B. lactis aerogenes*, respectively, are only exceptionally passed over in similar experiments. On the other hand, in monkeys intravenously inoculated with the virus of poliomyelitis, spinal drainage was not sufficient to carry over the infection, while in cats the same procedure produced a *B. lactis aerogenes* meningitis in every experiment. It is therefore impossible, in experiments of this sort, to predict the effect of any procedure designed to affect the meningeal defense against any organisms or substances in a given animal when the prediction is based merely upon similar experiments in an animal of another species.

Thus it cannot be argued that spinal drainage, or the production of aseptic meningitis, or similar procedures will cause alterations in the human meningeal defense mechanism, facilitating the passage of drugs from the blood-stream to the cerebrospinal fluid, on the basis of similar phenomena in animal experiments. Nor should we be justified in assuming that the same results obtained by these procedures in normal human individuals would be obtained in cases of neurosyphilis where meningeal conditions are already altered by the disease processes. It might be expected that the lesions present, to say nothing of alterations in the normal pressure relations, might cause marked changes in the functional activity of the defense mechanism. It is conceivable that in one case of neurosyphilis meningeal irritation might increase the permeability of the complex, in another leave it unaltered, and in a third even decrease it.

Investigations along these lines in the human subject, and especially the neurosyphilitic, are few. Regarding the passage of syphilitic antibodies it must be borne in mind that there is little definite knowledge on this point. Kolmer<sup>24</sup> and others have demonstrated agglutinins for *T. pallida* in immunized animals and Kolmer, Broadwell, and Matsunami<sup>25</sup> found that the sera of syphilitics in the later stages of the disease agglutinated culture pallida in about 84 per cent of the sera studied. Agglutinins in the cerebrospinal fluid were absent in the few cases tested. We have been unable to find references to studies calculated to demonstrate the presence or absence of agglutinins after meningeal irritation. We were successful in an attempt to demonstrate the passage of hemolytic amboceptor from the blood to the cerebrospinal fluid after meningeal irritation in only one of 12 cases.

As for arsenic, Mehrten and McArthur<sup>26</sup> found that intravenous injection of arsphenamine resulted in a positive test for arsenic in 43 per cent of the spinal fluids withdrawn one hour later, and that the procedure of spinal drainage did not increase this percentage. When the intravenous injection was preceded six or eight hours by an intraspinal injection of

the patient's own serum, 92 per cent of the cases gave a positive arsenic test in the fluid, and the average amount of arsenic present was three times as great as in the controls. Hall and his associates,<sup>27</sup> using a similar technique, found that preliminary intraspinal injections did not increase the percentage of positive tests for arsenic nor the amount of the drug present. They criticize the work of Mehrten and McArthur on the grounds that the latter detected the presence of arsenic in amounts smaller than the delicacy of the test used would permit.

In a recent paper Dercum<sup>28</sup> states that spinal drainage is productive of as good, if not better, results than any method of intraspinal therapy. He contends that nutrition of the central nervous system is carried on by the perivascular, pericapillary, and perineuronal lymph spaces of the brain and cord; and that absorption of the cerebrospinal fluid and of various substances introduced into it takes place, in small part, at least, by way of these lymph channels. In this connection Sabin<sup>29</sup> and her co-workers were unable to demonstrate the existence of lymphatics in the central nervous system; and Dandy and Blackfan<sup>30</sup> concluded from their experiments with phenol-sulphonephthalein that the lymphatics play no part in the absorption of cerebrospinal fluid.

Dercum objects to intraspinal medication because substances introduced into the cerebrospinal fluid rapidly disappear into the general circulation; and because, even if they did not disappear, they could not penetrate to the diseased cells of the parenchyma. Dandy and Blackfan<sup>31</sup> have shown for internal hydrocephalus, and Mehrten and West<sup>32</sup> for other diseases of the central nervous system, notably neurosyphilis, that the time of appearance in the urine of phenolsulphonephthalein introduced subdurally is enormously prolonged over the normal. The total excretion, normally complete in about six hours, was also very much but not uniformly prolonged. This being true for a dye as diffusible as phthalein, it is reasonable to assume that the excretion of spirochaeticidal substances introduced is also much prolonged and that such substances may remain in contact with the diseased meninges for several hours at least.

That substances introduced subdurally can, under certain circumstances, reach the parenchymatous cells of the nervous system, is demonstrated by the results of treatment in poliomyelitis. The pathology<sup>33</sup> of poliomyelitis consists essentially of an acute interstitial meningitis, followed by extensive perivascular infiltration entering the parenchyma of the cord, and ultimately involving particularly the anterior horn cells and the posterior root ganglia. Brain, cerebellum and medulla

<sup>24</sup> Sabin, F.: Johns Hopkins Hospital Reports, Monographs, New Series, No. V, 1913.

<sup>25</sup> Dandy, W. E., and Blackfan, K. D.: Am. J. Dis. Children, 1914, VIII, 406.

<sup>26</sup> Mehrten, H. G., and West, H. F.: Arch. Int. Med., 1917, XX, 575.

<sup>27</sup> Peabody, F. U., Draper, G., and Dochez, A. R.: Monographs of the Rockefeller Institute for Medical Research, 1912, No. 4, 18.

<sup>24</sup> Kolmer, J. A.: Jour. Exp. Med., 1913, XVIII, 18.

<sup>25</sup> Kolmer, Broadwell, and Matsunami: Jour. Exper. Med., 1916, XXIV, 333.

may be similarly involved. Amoss and Chesney<sup>27</sup> have demonstrated the curative effect of combined intraspinal and intravenous injections of immune poliomyelitis serum. The mechanism by which benefit is effected—whether it be by direct action of the serum on the virus of poliomyelitis within the diseased tissue, or whether the irritation of the intraspinal injection opens the pathway for the passage of immune bodies from the blood—is here beside the point. The fact remains that in some way the parenchyma of the nervous system is reached and benefit ensues.

Parenchymatous neurosyphilis is practically always associated with syphilitic disease of the meninges, and in a large

<sup>27</sup> Amoss, H. F., and Chesney, A. M.: *Jour. Exp. Med.*, 1917, XXV, 581.

proportion of neurosyphilitics meningitis is the principal if not the sole disturbance. It is these very cases—early tabes dorsalis, cerebrospinal syphilis, or very early asymptomatic neurosyphilis—in which the greatest benefit is to be derived from intraspinal therapy.

#### CONCLUSIONS

1. Intraspinal therapy is a necessary and rational adjunct in the treatment of neurosyphilis in cases which fail to respond to routine antisyphilitic treatment.
2. The mode of action of intraspinal medication does not depend upon increased permeability of the meninges.
3. Aseptic meningitis produced by intraspinal injection of irritants may prove an untoward rather than a beneficial factor in the treatment of neurosyphilis.

## MONONUCLEAR LEUCOCYTOSIS IN REACTION TO ACUTE INFECTIONS

### (“INFECTIOUS MONONUCLEOSIS”)

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A mononuclear leucocytosis in children is not unusual, and when it occurs is a simple lymphocytosis showing almost exclusively normal lymphoid forms or cells varying but slightly from them in morphological characteristics. In adults also one may encounter occasionally a mononuclear leucocytosis, but the picture presented is different from that seen in children in that the increase in leucocyte count is due largely to pathological forms of diverse morphology, probably all lymphoid in origin but not proven so. Such a blood picture may be seen in a variety of conditions, but among them there are some that show not only the same blood picture but other signs and symptoms so much alike that they seem to constitute a group by themselves.

During the past few years we have observed several cases in adults presenting the symptoms of an acute infection, a moderate enlargement of the lymph nodes and of the spleen, and a mononuclear leucocytosis instead of the more usual increase in the polymorphonuclear leucocytes. Similar cases have been described by Türk,<sup>1</sup> Lüdke,<sup>2</sup> Marchand,<sup>3</sup> Cabot,<sup>4</sup> Sanders<sup>5</sup> and others, and most of these authors emphasize the resemblance of such cases to acute leukaemia. Türk considered this group of cases as a key to the understanding of acute leukaemia and upon it are based arguments for the infectious nature of the acute leukaemias by those who favor that theory. Although these reports have been in the literature for some time, such cases are not very generally recognized and each new one is apt to give rise to grave apprehension of the onset of a leukemic state. Hodgkin's Disease, also, has usually been suggested as a possible diagnosis during the observation and study of cases of this series. The close similarity to each other in symptomatology, in physical find-

ings, and especially in haematology, gives these cases a well-defined position as a fairly clear-cut clinical group, whether or not they may form an entity from the viewpoint of etiology. A better appreciation of this syndrome is desirable, not only for the sake of accuracy in diagnosis but also because in this relatively benign affection a favorable prognosis may be given.

#### CASE I

H. C. Medical No. 31625. White woman, unmarried. Age 23 years. Medical student. Admitted to the hospital October 24, 1913. Discharged November 18, 1913. Acute febrile disease without local manifestations except marked lymphocytosis and slight enlargement of lymph nodes and spleen. Recovery.

*Complaint.*—Headache and backache.

*Family History.*—Unimportant.

*Personal History.*—The patient had had measles and scarlet fever in childhood, smallpox in 1907—mild, and frequent attacks of inflammatory rheumatism, the last one four years ago. Until the tonsils were removed five years ago, there were repeated attacks of tonsillitis. Otherwise the personal history was negative.

*Present Illness.*—The patient had been feeling badly for several days, but was not sick. The day before admission there appeared suddenly an occipital headache and chilly sensations. When the patient was admitted to the hospital she had headache, aching in the back and some pain in the left side.

*Physical Examination.*—On admission (summary): T., 102°; P., 80 per min.; R., 26 per min. The patient was a little dull. Her face was flushed. There was slight photophobia and conjunctivitis. The thyroid isthmus was enlarged but there was no bruit. At the apex of the right lung the breath sounds were harsher and expiration was longer than on the left. The percussion note on the right at the apex was a little shorter than on the left. Relative cardiac dulness extended 11.5 cm. to the left and 4 cm. to the right of the mid-sternal line. The first sound at the apex was slightly booming in quality and was followed by a

well-marked systolic blow. There was general tenderness over the abdomen but no resistance or spasm, and the right kidney was palpable. The liver was 2 cm. below the costal margin in the mid-clavicular line. The spleen was not palpable.

On the next day, chains of firm, discrete, slightly tender lymph nodes were noted in the left anterior and posterior cervical triangles. On October 30, one week after the onset, a pharyngitis appeared and there was moderate enlargement of lymph nodes in all the cervical regions and in the axillæ, slight impairment of the percussion note over the manubrium and an enlarged area of splenic dulness which reached nearly to the costal margin. The edge of the spleen could not be felt. Although the blood had been repeatedly examined for malarial parasites both in fresh and in stained preparations, the abnormal differential formula of the leucocytes was not noted until this day, when a well-marked lymphocytosis was present.

*Blood.*—Numerous examinations for malarial parasites were negative. Blood cultures and Wassermann reaction were negative. The bleeding time was slightly prolonged. The record of the blood examination is shown in Chart I.

*Lymph Nodes.*—A chain of nodes was removed from the neck on October 11. They were soft, friable and on section more nearly uniform than the normal tissue.

1. A piece was ground up in salt solution and injected into the peritoneal cavity of a guinea-pig with negative results.

2. Cultures were made on blood agar and on Loeffler's serum and incubated for many days without growth.

3. Sections were prepared for histological study and examined by Professors Welch and Whipple. The lymphoid tissues showed no follicles and no increase in fibrous tissue. The lymph cords were distinct and mitotic figures numerous. The sinuses were filled with many lymphoid and some endothelial-like cells.

BLOOD CHART.—CASE I

Date.....	10-30-13	11-4-13	11-6-13	11-10-13	11-17-13	12-6-13	1-6-14	1-7-14	11-6-14	3-26-15	4-30-20
R. B. C. ....	5,072,000	....	....	....	5,376,000	....	....	....	5,104,000	5,400,000	4,892,000
Hb. %.....	90	....	92	....	96	....	....	....	90	90	75
W. B. C. ....	10,000	17,500	13,920	9,800	9,200	9,000	8,700	13,500	6,800	6,000	5,200
P. M. N. %.....	24.	....	19.3	14.3	26.	21.2	46.6	75.	63.5	56.	65.
P. M. E. %.....	.8	....	.0	....	.3	.4	.3	....	....	....	1.
P. M. B. %.....	.4	....	.3	.3	.6	.8	.3	.3	1.	1.	1.
Small lymphocytes %.	57.2	....	28.6	66.6	62.6	69.2	44.6	16.6	26.	17.	16.
Large lymphocytes %.	....	....	36.	15.6	2.6	6.	4.3	3.6	....	8.	10.
Large mononuclears %.	14.	....	1.6	2.	.6	1.2	3.	2.6	2.5	5.	3.
Transitional % ..	1.6	....	4.	....	2.	....	.6	.6	4.	2.5	2.
Unclassified %....	.8	....	10.	1.	5.	1.2	....	1.	3.	10.	2.
Myelocytes %....	.8	....	.6	....	....	....	....	....	....	....	....
Clinical condition.	Febrile.	....	Subjectively much improved.	Convalescent.	Convalescent 2 days before discharge from hospital.	Convalescent.	Apparently well.	Acute tonsillitis.	Well.	Indisposition with tender cervical lymph nodes.	Five years after recovery.

On November 4, the white blood count reached its highest point, 17,500, and the cervical nodes had increased in size. The spleen was felt on November 10. On November 6, the temperature had fallen almost to normal and subjectively the patient was much improved. Convalescence was uneventful. When discharged from the hospital there were still many slightly enlarged nodes in the neck and axillæ, slight impairment of the percussion note over the manubrium, and increased splenic dulness. The leucocytes numbered 9200 with the lymphocytes 65 per cent. The systolic blood pressure was 115 mm. Hg., the diastolic 75. When the temperature was high, the pulse rate varied from 100 to 120 per minute.

*Laboratory Data.*—There was no sputum. A throat culture on November 4, when there was a complaint of sore throat, showed only the usual flora. Urine and feces were normal.

The von Pirquet tuberculin test was considered faintly positive on November 2, but on repetition on November 19 was quite negative.

An X-ray examination of the thorax revealed nothing unusual. There was slight thickening of the mediastinal tissues and a moderate chronic infiltration of both lungs, more marked on the right.

Neither eosinophiles nor giant cells were found. While no diagnosis was made, it was agreed that such a picture might be found in a lymphatic leukaemia.

*Subsequent Course.*—The patient has been under observation for six years. Examinations of the blood were made at intervals as shown in the table. On January 6, 1914, the polymorphonuclears and mononuclears were about equally divided. Ten days later, during a mild tonsillitis, the blood picture showed the usual polymorphonuclear reaction to such infections. One year after this illness her general health was excellent, lymph nodes in the neck and axillæ were just palpable, there was no demonstrable splenic enlargement and the heart was quite clear. The blood was normal.

During the six years since the illness reported here the patient has worked hard as a medical student, interne and laboratory worker. She is at present entirely normal and shows a normal blood picture.

The second case differs from the first in that it presented a more prolonged and less acute febrile period.

## CASE II

*R. L. R.* Medical No. 34068. White man, unmarried, age 24 years. Medical student. Admitted to hospital April 20, 1915. Discharged June 10, 1915. Febrile disease of about 10 weeks duration with lymphocytosis and enlarged spleen. Recovery.

*Complaint.*—Chills, fever, loss of weight.

*Family History.*—Unimportant.

*Personal History.*—The patient had had measles, mumps and whooping-cough as a child. Otherwise negative.

*Present Illness.*—The present illness began insidiously about one month before he entered the hospital, and was considered an ordinary attack of "La Grippe" because of the "cold in the head," headache, soreness in chest, neck and back, and general malaise. For three days there was a chill each evening about 7 p. m. The temperature was not taken. After three days in bed and a few doses of aspirin and quinine he felt well, returned to work and was apparently quite normal for four days. The symptoms then returned, soreness, anorexia, a chill each day at 7 p. m. and fever which increased a little each day until it reached 102° at 10 p. m. two days before admission to the hospital. There was slight constipation, no cough, no pain in the abdomen or chest. Quinine had no apparent effect.

*Physical Examination.*—On admission (summary): T., 101° F.; P., 112 per min.; R., 18 per min. The patient was a well-nourished young man. He looked sick. The tonsils were not enlarged or inflamed. The lymph nodes under the angles of the jaw were palpable. The chest was clear. The abdomen was distended. The spleen was palpable just below the costal margin. It had a rounded edge, was firm and rubbery. The thyroid isthmus was palpable and there was fulness over the lobes. There was some tremor of the fingers and sweating of the hands.

*Laryngoscopic examination* (Dr. Crowe) was negative except for chronic infection of the right tonsil.

*Laboratory Data.*—The urine and stools were normal. Calmette 1 per cent tuberculin reaction was negative. X-ray examination of the thorax showed clouding of both apices, slight infiltration of both upper lobes and slight pleuro-diaphragmatic adhesions on the right side. X-rays of the paranasal sinuses were negative.

*Blood.*—Cultures from the blood on April 20 and on May 25 were sterile. The Wassermann reaction was negative. Repeated tests for agglutinins for *B. typhosus* and *B. paratyphosus* were negative. Malarial parasites could not be found either in ordinary smears or in thick films prepared by the Ross method.

There was a continuous fever for the first three days and then it became intermittent for about three weeks, reaching 101° F. in the evening and about 99° F. in the mornings. It then became remittent and the patient was discharged at the end of seven weeks with a slight evening fever (99° F.).

The spleen was palpable throughout the patient's stay in the hospital and was palpable on discharge. The enlargement of the glands had disappeared.

This patient finished his course in medicine, served a term as medical officer in the army and now, four years after this illness, is a practising physician.

The main interest is in the blood picture. See Chart II.

## CASE III

*H. B. G.* Medical No. 37257. White woman, unmarried. Age 29 years. Medical student. Admitted to hospital February 5, 1917. Discharged February 19, 1917. Diagnosis: Acute infection, pharyngitis, adenitis.

*Complaint.*—Headache and general malaise.

*Family History.*—Unimportant.

*Personal History.*—The patient has had measles, mumps and varicella in infancy, malaria at three years of age, and for years an annual attack of tonsillitis.

*Present Illness.*—The present illness began about three weeks before the patient's admission to the hospital with headache, swelling of the glands of the neck, and a slight cough. She was kept in bed at home under supervision. Finally, the muscles of the neck and shoulders became sore and tender, the cervical glands became tender also and the patient was admitted to the hospital.

## BLOOD CHART.—CASE II

Date.....	4-20-15	4-25-15	5-10-15	5-31-15	6-8-15
R. B. C.....	5,328,000	.....	.....	.....	4,184,000
Hb. %.....	88	.....	.....	.....	91
W. B. C.....	6,620	7,000	6,800	9,320	7,800
P. M. N. %.....	40.8	.....	.....	26.6	28.8
P. M. E. %.....	.0	.....	.....	.0	.0
P. M. B. %.....	0.4	.....	.....	.0	.4
Small Lymphocytes %.....	34.	.....	.....	56.7	49.6
Large Lymphocytes %.....	18.	.....	.....	12.7	3.6
Large Mononuclears %.....	..	.....	.....	.....	1.2
Transitional %.....	6.8	.....	.....	4.0	7.6
Unclassified %.....	....	.....	.....	....	8.8
Myelocytes %.....	.0	.....	.....	.0	....

*Physical Examination.*—On admission (summary): T., 99.5°; P., 100 per min.; R., 28 per min. She was a well-nourished young woman and looked ill. The tonsils were small, adherent and showed many small crypts. The pharynx was injected and showed a rather marked lymphoid hyperplasia. The posterior and anterior cervical, submaxillary, axillary and inguinal glands were palpable, firm and tender. The chest was clear and the heart and abdomen negative. The spleen was not felt. The urine examination was negative.

## BLOOD CHART.—CASE III

Date.....	1-22-17	1-24-17	2-5-17	2-17-17
Total W. B. C.....	11,800	10,000	10,400	17,280
Differential:				
P. M. N. %.....	59	45	42	43.4
P. M. E. %.....	1	2	4.8	4.4
P. M. B. %.....	0	0	.0	.2
S. L. %.....	12	27	20.8	22.2
L. L. %.....	12	13	23.2	20.2
L. M. Transitionals %.....	16	9	8	8.2
Unclassified %.....	0	0	.0	1.4

There was an intermittent fever for four days after admission, reaching 100° F. in the evenings and being normal in the morning. For the following 10 days while she remained in the hospital the temperature was normal.

*Blood.*—See Chart III.

Since her discharge from the hospital, the patient has remained well. She finished her course in the medical school and is now an interne in a hospital.

## CASE IV

S. H. H. Medical No. 42775. White man, unmarried. Age 25 years. Medical student. Admitted to hospital October 17, 1919. Discharged November 26, 1919. Diagnosis: Adenitis, infectious mononucleosis.

**Complaint.**—Headache and swelling of the glands at the angles of the jaw.

**Family History.**—Unimportant.

**Personal History.**—The patient has had mumps, measles, and whooping-cough in childhood and an occasional sore throat. He was in the hospital in November, 1917, with a chronic bronchitis. Tuberculosis was considered at this time, but was fairly definitely excluded.

**Present Illness.**—Three weeks before his admission to the hospital the patient noticed while shaving that the glands under the angles of the jaw were swollen. A few days later he began to have headache and general malaise which gradually increased in intensity until his admission to the hospital.

**Physical Examination.**—On admission (summary): T., 100.6°; P., 80 per min.; R., 22 per min. The face was slightly flushed, the skin moist and hot, the pharynx injected and showing a slight muco-purulent exudate over the posterior pharyngeal wall. The tonsils were slightly enlarged and hyperemic, but without exudate. The posterior and anterior cervical, axillary, inguinal, and epitrochlear glands were palpable, of a rubbery consistence, and were slightly tender. The chest showed signs of fibrosis at the right apex. The heart was normal. The spleen was palpable one finger's breadth below the costal margin.

The urine and stool examinations were negative. The Wassermann test, a blood culture and an X-ray of the chest were negative. The throat culture showed a non-hemolytic streptococcus.

Several days after admission the patient developed pus crypts in the tonsils.

A cervical gland was removed for study on October 20, 1919.

**Report by Dr. Martzloff.**—“Section of lymph gland in which normal lymphoid architecture is lost. The lymph sinuses are engorged. There are many large cells with round or oval nuclei that are pale-staining. Numerous polymorphonuclear neutrophile and transitional cells, and occasional eosinophile cells are seen. There is an increase in lymphocytes. No areas of necrosis or invasion are present. No giant cells or Dorothy Reed cells are seen. Impression: Lymphadenitis.”

**Report by Dr. Bloodgood.**—Dr. Bloodgood agreed with the above report and raised the question if this might be a very early Hodgkin's Disease, earlier than has ever before been studied histologically.

Temperature readings showed an intermittent fever for 16 days, reaching 101° F. in the evening, becoming normal on the seventeenth day in the hospital; and then, except for several days when there was one-half degree elevation, remaining normal.

**Blood.**—See Chart IV.

Since his discharge from the hospital more than six months ago, the patient has been well. He now has a slight general glandular enlargement, but his spleen is no longer palpable and the blood picture has become normal.

## CASE V

White man, unmarried. Age 28 years. Banker. This patient was a private patient of Dr. Lawrence Getz, who gave the authors all the clinical data and supplied blood specimens for study.

**Complaint.**—Headache and general malaise.

**Family History.**—Unimportant.

**Personal History.**—The patient had a guillotine tonsillectomy in childhood. Otherwise the history is unimportant.

**Present Illness.**—Three days after having been chilled at a football game the patient went to bed with fever and general

malaise, headache, anorexia, and photophobia. Three days later rigidity of the neck developed. At this time on examination the spinal fluid was normal. Six days after the onset the patient developed a sore throat involving uvula, soft palate, pharyngeal walls and tonsillar tissue. At this time there was tenderness over the sides of the face.

**Physical Examination.**—At the onset there was flushing of the face, fever, prostration, slight conjunctivitis, and some little swelling of the lower face and neck. The heart and lungs were clear. The abdomen was negative.

The rigidity of the neck developing three days later was probably associated with the tenderness and swelling of the glands and tissues of the neck. The injection of the uvula, soft palate, pharyngeal walls and bits of tonsillar tissue was present six days after onset.

Early in the illness the anterior and posterior cervical and the axillary glands were palpable, slightly enlarged, firm and a little tender. The spleen became palpable several finger-breadths below the costal margin, was firm and had a rounded edge. It remained palpable throughout the course of the illness.

The urine showed a faint trace of albumin and a few granular casts. The spinal fluid was normal. Two blood cultures were negative.

The temperature showed remittent fever for a few days and then became intermittent in type. The highest evening temperature was 102.8° F. shortly after the onset. After 17 days the temperature became normal for the whole 24 hours and remained normal until recovery was complete.

**Blood.**—See Chart V.

Since recovery the patient has been well and has been carrying on his usual occupation. Examination on April 11 showed that there was no glandular enlargement and the spleen was not palpable. The blood picture was normal.

Through the courtesy of Dr. Barker the following case from his private clinic was studied:

## CASE VI

A young woman, Medical No. 5905, 20 years of age, from a distant state, was observed in October, 1919, during convalescence from an acute infection associated with lymphadenopathy and lymphocytosis.

**Complaint.**—At this time was of fatigue and drawing sensations in the left leg, especially at night.

**Past History.**—The patient's health has been good with the exception of tonsillitis because of which a tonsillectomy was done two years ago. She suffered from occasional headaches, rather frequent colds, constipation and dysmenorrhea.

**Present Illness.**—The present trouble began about two months before and was characterized by asthenia, malaise, fever for three weeks with the temperature ranging from 99° to 102°, a general glandular enlargement and a leucocytosis of 17,000 with the following differential count of 500 cells: P. M. N., 16.4 per cent; P. M. E., 0.4 per cent; P. M. B., 0.2 per cent; small lymphocytes, 77.5 per cent; large mononuclears, 1.6 per cent; transitorials, 3.6 per cent.

In the examination in Dr. Barker's clinic three or four weeks after the cessation of the fever the essential findings, outside the blood and hematopoietic system, were undernutrition to the extent of about 15 pounds; a thickened thyroid isthmus and pulse rate of 100; unerupted upper third molars; gastric hypochrondria, slight tenderness in the right lower quadrant of the abdomen, overfilling of the cæcum and spasticity of the colon.

The spleen was not palpable nor apparently enlarged on percussion.

There was very slight general lymph glandular enlargement, including the cervical, axillary, epitrochlear, peribronchial and

## BLOOD CHART.—CASE IV

Date .....	10-17-19	10-20-19	10-21-19	10-22-19	10-23-19	10-24-19	10-26-19	10-29-19	11-3-19	11-10-19	11-15-19	11-21-19	12-22-19	4-5-20
R. B. C.....	5,240,000	....	....	5,560,000	....	....	....	6,072,000	....	5,600,000	5,760,000	5,968,000	....	5,744,000
Hb. %.....	98	....	....	98	....	....	....	98	....	100	100	100	....	100
W. B. C.....	7,800	18,820	18,560	20,800	17,400	10,820	8,160	11,240	8,020	8,400	12,700	9,800	9,000	8,900
P. M. N. %.....	22.5	21.5	29.5	27.	30.	34.5	19.	49.	48.5	59.	56.	59.	66.5	75.
P. M. E. %.....	2.5	1.5	0.5	2.0	4.0	4.5	1.0	9.	5.0	6.0	9.0	12.0	6.0	5.
P. M. B. %.....	.0	.0	.0	.0	.0	.0	1.	1.	1.5	2.0	.0	.0	.0	0.
S. L. %.....	14.5	19.0	42.	45.5	40.	49.	66.	26.	34.	25.	25.	25.	3.5	8.
L. L. %.....	.0	.0	24.	21.5	22.	9.5	7.5	11.	6.5	4.5	4.	1.	13.5	7.
L. M. %.....	13.5	8.0	3.0	3.0	2.0	1.0	1.0	3.0	3.0	1.5	1.0	1.0	3.5	0.
Trans. %.....	9.5	7.0	1.0	1.6	.0	1.0	1.0	1.0	1.5	2.0	5.0	2.0	3.5	2.
Unclass. %.....	37.5	43.0	....	....	....	....	1.0	....	....	....	....	....	....	3.
Myelocytes %.....	....	....	....	....	2.0	....	1.0	....	....	....	....	....	....	....
Myeloblasts %.....	....	....	....	....	....	1.0?	....	....	....	....	....	....	....	....
Remarks .....	On admission.	Pus crypts in tonsils.	....	Highest fever recorded.	....	....	....	....	Slight evening fever.	....	Afebrile.	....	....	4 months after recovery.

## BLOOD CHART.—CASE V

Date .....	11-28-19	11-29-19	12-3-19	12-5-19	12-7-19	12-9-19	12-11-19	12-14-19	4-11-20
R. B. C.....	....	4,516,000	5,120,000	4,672,000	4,172,000	3,800,000	4,400,000	4,656,000	4,920,000
Hb. %.....	....	103	....	....	....	....	....	....	98
W. B. C.....	6,500	6,200	17,120	18,420	18,460	11,825	9,700	6,600	5,080
P. M. N. %.....	....	49.6	23.8	28.5	24.0	28.0	32.0	22.1	56.
P. M. E. %.....	....	3.2	2.0	0.7	1.0	1.0	0.7	0.7	7.
P. M. B. %.....	....	.0	.0	0.7	.0	0.5	.0	0.7	1.
S. L. %.....	....	23.0	12.3	21.4	22.0	13.5	10.0	11.5	19.
L. L. %.....	....	17.6	43.8	28.5	36.0	48.0	49.2	50.4	6.
L. M. %.....	....	3.2	11.5	7.2	5.0	9.	7.4	0.7	3.
Trans. %.....	....	2.4	6.	7.2	4.0	9.	7.4	13.7	5.
Unclass. %.....	....	.0	.0	.0	7.0	.0	.0	.0	3.
Myelocytes %.....	....	.0	.0	5.0	1.0	.0	.0	.0	....
Remarks .....	....	Rigidity of neck. Lumbar puncture.	Pharyngitis. Swelling of neck and face.	....	....	....	Temperature normal.	....	4 months after recovery.

inguinal groups. A gland was excised from the region of the scapula, histological preparations were made and the following reports received:

From Dr. W. G. McCallum.—“The lymph gland is not especially enlarged; in general its architecture is maintained. One can see the peripheral sinuses quite plainly. There is, however, a great enlargement of the lymphoid tissues proper so that the interior of the gland tends to become a solid mass. The distinction between the germinal centers and the peripheral part of the lymph cord can still be made out. The sinuses contain many free cells, but are not packed with them. Most of these are small cells with deeply stained round nucleus and, although with this fixation practically nothing can be seen of their cytoplasm, they look like lymphocytes. There is some infiltration of these same cells in the capsule of the gland and there are lymphatics there which are filled with them. In the periphery the lymphoid cells are practically pure around the margin of the lymph cord, while the center is made up of larger and paler cells. There is one quite large area which seems to be more diffusely made up of these larger cells, which might be called reticulum cells. Among these are a few lymphoid cells, most of which are fragmented.

“There is nothing about this gland which would allow anyone to make a definite diagnosis. It appears, however, that several things can be excluded. It has not the structure of Hodgkin's Disease; there is no such tumor growth or infiltration as would suggest strongly a lymphosarcoma. The condition is consistent with the diagnosis of lymphocytic leukæmia, but, if so, it must be a very early stage or else in a period of recovery.”

From Dr. Joseph Bloodgood.—“There is nothing in the sections that would allow a positive diagnosis. The histology of the gland is not normal. It suggests an acute rather than a chronic process.

“There is no endothelial hyperplasia or increase of stroma. There are no tubercles or giant cells and no definite Dorothy Reed cells.

“The marked features are increased vascularity of the capsule and apparently proliferation of the lymphoid cells, which are a little larger than in a normal resting gland. On the whole there is slight obliteration of the stroma of the gland and endothelial-lined spaces.

“One could not exclude lymphosarcoma. In leukæmia the lymph glands have this appearance, but when lymph glands are removed for other acute infections not pyogenic, they are difficult to differentiate from the gland in sarcoma or leukæmia.

“The diagnosis in a case of this kind must rest upon the blood picture.”

*Blood.*—On examination showed:

(a) R. B. C., 4,496,000. Hb., 85 per cent. W. B. C., 9000 with the differential formula: P. M. N., 56.4 per cent; P. M. E., 0; P. M. B., 0.8 per cent; S. M., 34 per cent; L. M. and T., 8.0 per cent. The red cells were a little pale, otherwise normal; the platelets were normal in number and no abnormal cells were seen.

(b) The Wassermann reaction was negative.

(c) The blood culture was negative.

All these cases were in young adults. Each ran a febrile course. In two the onset was rather sudden; in the other four there was a prodromal period of three or four weeks. The symptoms were those of an obscure infection without marked localization in two cases. Of the others two showed definite evidences of upper respiratory tract infection and two symptoms suggesting, in addition, a myositis of the neck and shoulder region. Two patients had conjunctivitis and photophobia. All showed enlarged and tender cervical glands and five of the six had, in addition, enlarged and slightly tender glands in the axillary and inguinal regions. In four

cases the spleen was palpable but in none was it markedly enlarged; when palpated it felt hard and rubbery. In none of these patients could tuberculosis be demonstrated and, although three showed a slight enlargement of the thyroid gland, there was no evidence of active thyroid disease or status thymico-lymphaticus. The temperature in the five febrile cases followed from the onset, was remittent or intermittent with a rise to 101° to 103° in the evening. One case showed an evenly elevated temperature for three days, after which the intermittent course appeared. The average duration of fever was between two and three weeks.

The urine of one patient showed albumin and casts, but urine examinations in the other cases were negative. Stool examinations were negative in all. None showed a positive Wassermann test. In the four cases in which blood cultures were made, they were negative. Throat cultures were made in two of the cases, one of which showed a non-hemolytic streptococcus. Culture of the cerebrospinal fluid in one case was negative. Animal inoculation of a gland in one case failed to disclose a definite etiological agent.

The blood picture in all the cases observed from the beginning (Cases I to V, inclusive) was the same, showing variations hardly even in minor points. For the first few days the total white blood cell count was normal or only slightly increased. Then followed a leucocytosis of from thirteen to twenty thousand cells per cubic millimeter. The differential counts showed that the percentage of mononuclear elements was increased and that when the leucocytosis occurred it was due largely to an increase in these cells. The small lymphocytes and to a less extent the cells of the large mononuclear-transitional group (the granular mononuclears of normal blood)\* were increased, but the chief changes were due to the presence of those cells designated (for want of a better name) by the term “large lymphocytes.” Under this heading were included all mononuclear cells seen that were not small lymphocytes or those of the large mononuclear-transitional group. Among these were cells (see plate) differing from a true lymphocyte only in that they had a finely reticulated, purplish-staining nucleus.\* Others with the same type of nucleus were large and had an abundant protoplasm which was stained either a deep, dark blue or a clear, pale blue. There were large cells with deeply staining blue-black, pyknotic nuclei, showing the same variations in the protoplasm as the cells with the finely reticulated, purple-staining nucleus. Some few showed an occasional azurophilic granule, but these were the exception. An occasional cell showed the clover-leaf, so-called Rieder nucleus. In other words, all types of pathological lymphocytes, some resembling Türk's irritation forms, were to be seen. None of those so studied showed granules with the Ehrlich stain or contained an oxydase ferment as demonstrated by Graham's' method. Just what is the significance of these cells cannot be stated at present, but they are generally accepted as lymphoid in origin. The red blood cell counts, hemoglobin determina-

\* Wilson's modification of the Romanowsky stain was used for the routine preparations.

tions, and studies of the platelets, show no deviation from the normal other than is to be expected in a very mild, slowly developing secondary anaemia incident to an acute infection. In the three cases in which it was possible to follow the blood picture for a long period the pathological lymphoid cells were found present for some weeks after the disappearance of other signs and symptoms, but eventually the blood returned to normal. It was at this stage that Case VI, diagnosed largely from the history and data afforded by her physician in a distant state, first came under observation here.

There is nothing distinctive in the changes in the lymph glands beyond a rather definite hyperplasia of the lymphoid cells. The sections from the three cases examined are quite similar, with minor variations due to the difference in the stage of the disease when the glands were excised. It will be seen that the reports from the several pathologists agree closely. There is no indication of Hodgkin's Disease, tuberculosis, or lymphosarcoma, and no definite histological distinction can be made between the glands in this group and in lymphatic leukaemia save in the degree of hyperplasia.

The frequency of pharyngitis and slight tonsillitis and the early enlargement of the cervical nodes point toward the respiratory tract as the atrium of infection. The sequence of events, which can be followed especially well in the first case, is interesting. With the onset of the symptoms of infection there may be a slight leucopenia. Then come the swelling of the lymph glands and the gradually increasing lymphocytosis and enlargement of the spleen. The height of the lymphocytosis and of the glandular and splenic enlargement may be reached at the end of the febrile period and these features persist to a certain extent for weeks after the patient is symptomatically well. The suggestion is obvious that the poison causing the disease produces first a slight damage to the blood-forming organs followed by evidences of stimulation of the lymphoid elements which continues for some time after the intoxication has apparently ceased. A phenomenon somewhat similar in kind but less in degree is seen in the leucopenia of typhoid and some other fevers followed by a post-infectious lymphocytosis.

One question naturally arises in this group of cases as well as in the leukaemias. Is the peculiar reaction due to any special quality in the exciting agent of the disease or is it referable to a definite tendency on the part of the reacting individual? Our data do not furnish a categorical reply to this question, but there is one interesting observation in the first case which may perhaps be accepted as bearing upon this point. Nine weeks after the temperature became normal the patient suffered from a typical attack of follicular tonsillitis with the usual polymorphonuclear leucocytosis. The count which preceded this one was made 11 days before and showed 52 per cent mononuclears in a total white count of 8700. This one observation would seem to indicate that there was no constant peculiarity in this individual's reaction to ordinary acute infections.

The differentiation from a beginning lymphatic leukaemia may be difficult. Fever, malaise and evidences of upper

respiratory tract infection are more or less characteristic of acute leukaemia. In that disease, however, with a low general leucocyte count one is apt to find a more marked anaemia, a tendency to hemorrhage, and many fragile cells with their resultant "smudges" in the blood smears. The cells which are not fragile are usually normal in appearance or, if not normal, are all of the same variety, while in the cases of infectious mononucleosis there is a diversity of types (see plates). The benign course with the early disappearance of fever and more gradual return of the blood picture to normal is the safest criterion and indeed the only one of any value in some of the reported cases which resemble leukaemia even more closely than those of this report. So close has been this resemblance in certain instances that eminent hematologists have considered the possibility of a leukaemia of transient nature from which the patient recovers spontaneously.

The differentiation from Hodgkin's Disease presents less difficulty. The blood picture is not strongly suggestive of that affection, the lymphatic enlargement is general rather than regional as is commonly seen in Hodgkin's Disease, and the histology of the excised gland does not suggest this diagnosis.

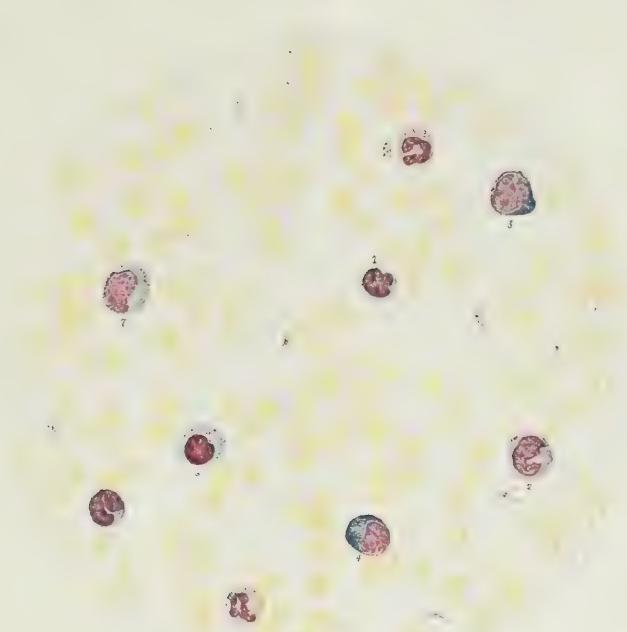
#### SUMMARY

The six cases presented in this paper exhibited a mononuclear leucocytosis in reaction to acute infection. The symptoms and signs in all are so nearly the same that they apparently constitute a distinct clinical syndrome. Each case ran a febrile course with moderately severe prostration. In four there were evidences of a tonsillitis or other infection of the upper respiratory tract, and a moderate general glandular enlargement. Four of the cases had, in addition, a palpable spleen. The total leucocyte count was normal at first, but later became moderately increased. The differential formula showed a slight increase in the cells of the large mononuclear-transitional group and the presence of many pathological lymphoid forms. Later there was a leucocytosis which was largely due to an increase in lymphoid cells among which were many pathological forms.

From a study of these cases no evidence has been adduced that they are dependent upon a single etiological factor. The data afforded by Case I, which showed a polymorphonuclear leucocytosis in reaction to an acute tonsillitis one year after the mononuclear leucocytosis, would suggest that this reaction is due to the character or peculiar action of the infecting organism rather than to a constant peculiarity of reaction in the infected individual.

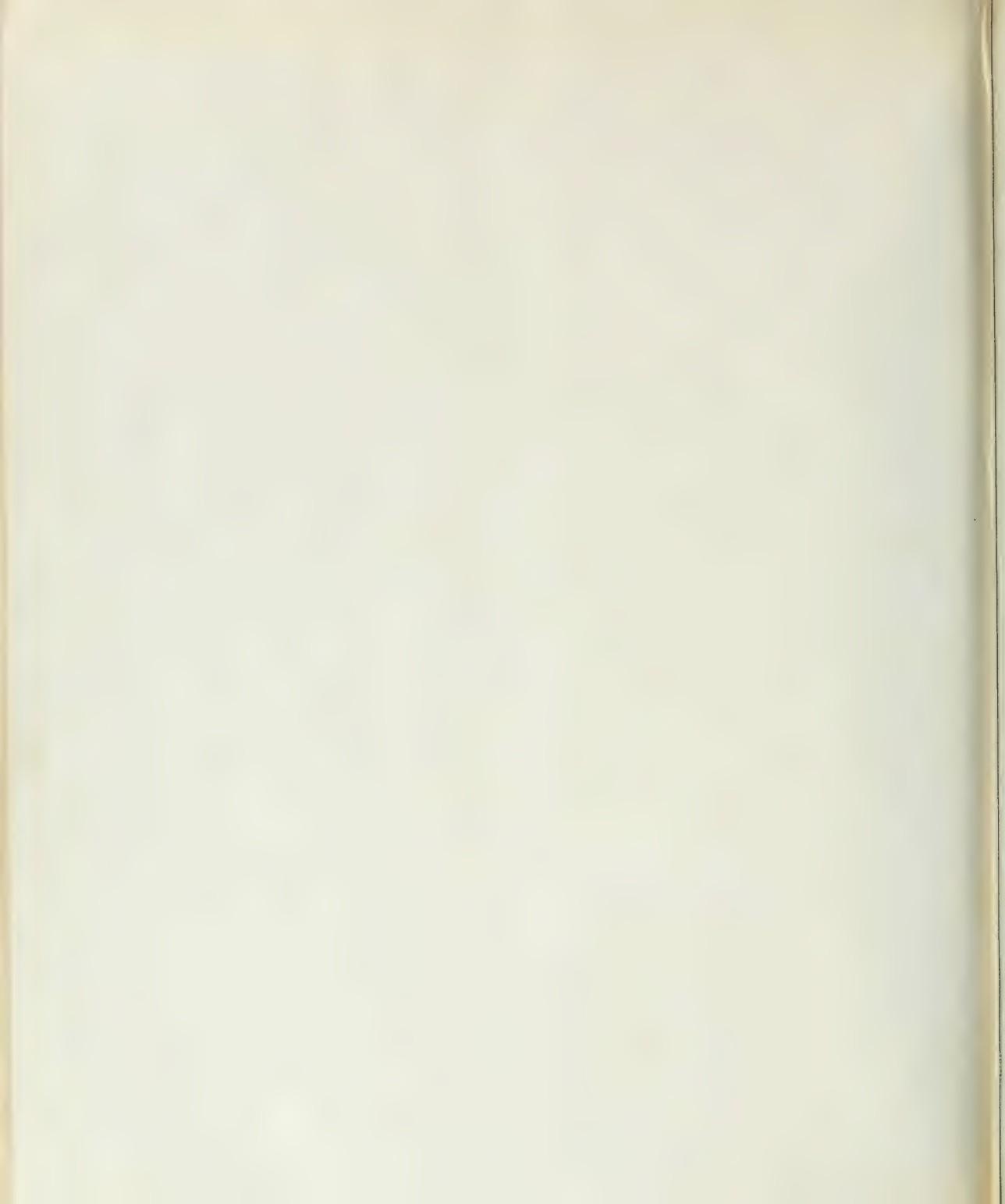
The information obtained from a study of these cases permits the following conclusions:

1. In addition to the mononuclear leucocytosis seen commonly in children one may encounter occasionally a mononuclear leucocytosis in adults in reaction to acute infection.
2. The mononuclear leucocytosis in adults in reaction to acute infection is not a simple lymphocytosis, as in children, but is made up largely of pathological forms, probably all lymphoid in origin.
3. Among the cases in adults presenting a mononuclear leucocytosis of this type there occurs a group with symptoms



COMPOSITE BLOOD FIELD DRAWN TO SHOW SOME TYPES OF LARGE MONONUCLEAR CELLS ENCOUNTERED IN THE MONONUCLEOSIS OF AN ACUTE INFECTION.

- (1) Small lymphocyte.
- (2) Cell of large mononuclear-transitional group.
- (3), (4), (5) Cell forms commonly seen in infectious mononucleoses, but rarely, if ever, in normal blood.
- (6) Large lymphocyte commonly seen in normal blood.
- (7) Large lymphocyte occasionally seen in normal blood.  
Wilson's modification of Romanowsky stain.



and signs so much alike that they may be considered provisionally as a clinical entity.

4. When first seen during the febrile period, especially in the early stages, these cases cannot be differentiated with assurance from leukæmia; but the subsequent course makes the diagnosis clear.

5. The prognosis, so far as may be judged from a series of six cases, is good.

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## PNEUMOCOCCUS TYPE I VEGETATIVE ENDOCARDITIS REPORT OF A CASE FOLLOWING AN ATTACK OF LOBAR PNEUMONIA

By HENRY M. THOMAS, JR., M.D., Resident Physician, AND DWIGHT O'HARA, M.D., Assistant Resident Physician

(From the Pneumonia Service of the Boston City Hospital.)

The case described in this report is of singular interest owing to its unusual clinical course and rare pathological findings. Presenting, as it did, difficult problems as to diagnosis and treatment, we feel that it will be of interest to all clinicians.

#### CASE REPORT.

M. O'H., 45, white, m., metal polisher. Admitted to Hospital May 19, 1920.

*Family History and Marital History* unimportant.

*Past History*.—Measles, whooping cough and scarlet fever as a boy. Pleurisy in 1917, ill 10 days. Influenza 18 months ago.

*Habits*.—Moderate use of tobacco, whiskey and beer, three or four drinks a day.

*Present Illness*.—Sudden onset three days ago with pain in the right side, which was increased on deep breathing. Cough with rusty sputum. Boneaches and vomiting.

*Physical Examination*.—Well developed and well nourished man, lying comfortably in bed. T. 104°, P. 100, R. 40.

Teeth, poor. Pharynx, injected.

Lungs. Emphysematosus. Signs of solidification of entire right lower lobe, and a small patch in the left lower lobe.

Heart and abdomen. Negative.

Remaining physical examination unimportant.

White blood count, 16,500.

May 20. X-ray report—Consolidation at right base and infiltration of right hilus.

May 21. (Sixth day of disease.) Report of sputum examination, Pneumococcus Type I. Report of blood culture, Pneumococcus Type I. Three doses of 100 c.c. of antipneumococcic serum, Type I, Massachusetts State Board of Health, given intravenously at eight-hour intervals, without reaction.

May 22. 4th, 5th and 6th doses of serum given, intravenously.

May 23. Temperature down to 100° (rectal) and pulse 80 per minute. The general condition seems much improved. Signs in lungs remain as on admission. Serum treatment suspended.

May 24. Temperature down to 98.6° (rectal) and pulse 75 per minute.

May 25. Temperature rose in the evening, but there were no subjective symptoms.

May 26. A diffuse urticaria developed over the extremities and body, and the temperature again reached 101° (rectal), in the evening. Physical examination reveals nothing new, and the temperature is thought to be due to serum sickness.

May 28. Serum sickness continues. Temperature 104° (rectal), this evening.

May 30. The patient seems better to-day. The lung signs are nearly as on admission, with perhaps a few more medium, moist rales in the right base behind.

June 1. The temperature remained down last night and to-day, but the patient does not seem to be improving.

June 3. For the past few days the patient's condition has not been improving, but repeated examinations fail to reveal any cause for the continued illness. There is some evidence of early resolution in the right lower lobe, and there is continued solidification in the left lower lobe. X-ray taken yesterday showed consolidation in right lung. A slight weakness on the right side of the face has been noticed, but consultation with the Neurological Service showed no definite involvement of the central nervous system. White blood count, 24,000.

June 5. A blood culture taken three days ago was reported positive for Pneumococcus Type I. Nothing new could be found to account for the septicæmia, but in view of the recent article by Blake and Cecil, in which they report observing pneumococcus septicæmia in monkeys for days after the crisis had occurred, it was decided to continue the intravenous treatment. For this purpose Mulford's Type I Antipneumococcus Antibody Extract was employed, in order to avoid anaphylactic shock from the use of horse serum, to which the patient was unquestionably sensitized by that time. Two doses of 100 c.c. were given intravenously without reaction.

June 6. 100 cc. Antibody Extract administered intravenously.

June 7. Following the treatment two days ago the temperature remained lower and the patient seemed somewhat improved, but yesterday afternoon he had a chill, after which his temperature rose to 104°. As our supply of Mulford's Antibody Extract was very small, it was decided to desensitize the patient for horse serum and to recommend intravenous serum therapy. The reason for this decision was that we hoped to combat the focus of infection, whatever it might be. Desensitization progressed rapidly without reaction until 10 c.c. were given intravenously.

This dose brought on a typical, mild anaphylactic reaction, which was controlled by adrenalin and atropine hypodermically. After this, 10 c.c., 15 c.c., 25 c.c. and 40 c.c. were given at hourly intervals without reactions.

June 9. Serum treatment continued yesterday and to-day. The patient's condition continues to become worse. A blood culture taken yesterday shows 3000 colonies per cc. of blood. The ears are negative. Neurological examination negative except for weakness of right facial muscles. The urine has been found negative repeatedly. An X-ray, taken June 7, suggested the possibility of a lung abscess in the middle of the right lung. At the angle of the right scapula the breath sounds have a somewhat amphoric quality, with medium to large consonating râles. The

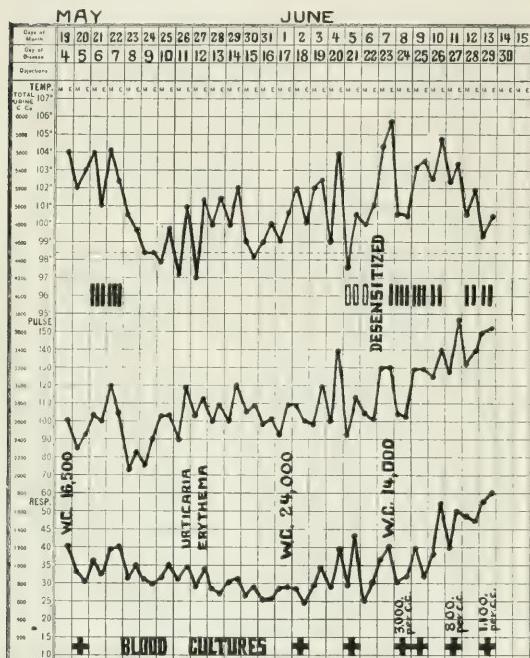


CHART I.—Clinical chart giving temperature, pulse, and respiration and indicating the points at which blood cultures were taken and serum treatments administered.

■ Indicates 100 c.c. of Antipneumococcus Type I horse serum.  
□ Indicates 100 c.c. of Mulford's Type Antipneumococcus antibody extract.

persisting signs at both bases and the bacteræmia are the only positive findings. There is no evidence of pericardial involvement, either by physical or by X-ray examination. In view of the fact that the original attack of pneumonia was apparently recovered from, the lung condition does not seem an adequate explanation for the septicæmia. In spite of the total absence of cardiac murmurs at any time throughout the course of the disease, an acute endocarditis may exist and be responsible for the present clinical picture.

June 11. As no apparent benefit has been derived from serum treatment at this stage of the illness, it is decided to modify the method of administration from three intravenous doses a day to one intravenous and one subcutaneous dose. Although little hope of benefit from serum is entertained, it is the only rational method

of treatment that occurs to us. The patient's condition continues to become worse. His only complaints are of extreme thirst and dryness of the mouth and throat. He takes fluids in large amounts and is given 4 ounces of whiskey a day.

June 13. Signs of solidification are more marked in both bases. To-day there is weakness of the left arm. The general condition is much weaker, and the terminal event seems a matter of hours. The septicæmia continues, having fallen to 800 colonies per c.c. on June 11.

June 14. The patient died this morning at 12.30 a.m. A blood culture taken yesterday shows 1100 colonies per c.c. of blood.

*Diagnosis.*—Lobar pneumonia—Right lower lobe. Left lower lobe, Pneumococcus Type I. Septicæmia, Pneumococcus Type I. Acute endocarditis (?). Lung abscess, right lower lobe (?). Brain Abscess (?).

*Autopsy Findings.*—At the post-mortem examination the following conditions were disclosed:

Lobar pneumonia of the left and right lower lobes, and the lower portion of the right upper lobe. Abscess of the right lower lobe, 4 x 3 x 2 cm. Hemorrhagic infarct of left upper lobe (small). Right and left healed pleurisy. Acute vegetative endocarditis of tricuspid valve. Focal meningitis. Chronic aortitis and arteriosclerosis. Acute splenic tumor.

The points of interest in the pathological findings of this case are several.

1. There was no gross evidence of resolution in any of the solidified areas of the lung tissue.

2. The endocarditis was limited to the tricuspid valve and had given rise at this point to a large vegetative mass (see Fig. 1), 4 x 3 x 1.5 cm., consisting of yellowish-grey, slightly friable tissue, over the surface of which there were small pinpoint reddish areas. Microscopically the vegetation was composed of masses of fibrin and cellular debris enclosing collections of gram-positive diplococci (see Fig. 2). The rest of the endocardium was free from acute lesions, nor was there any chronic endocarditis.

A few plaques of arterio-sclerosis were scattered over the mitral and aortic cusps.

3. The meningitis was localized to an area about 2.5 x 2 cm., near Broca's area on the antero-lateral aspect of the left hemisphere, consisting of greenish purulent material lying beneath the arachnoid but not extending into the brain tissue or displacing it. Smears from the pus showed gram-positive diplococci.

#### DISCUSSION.

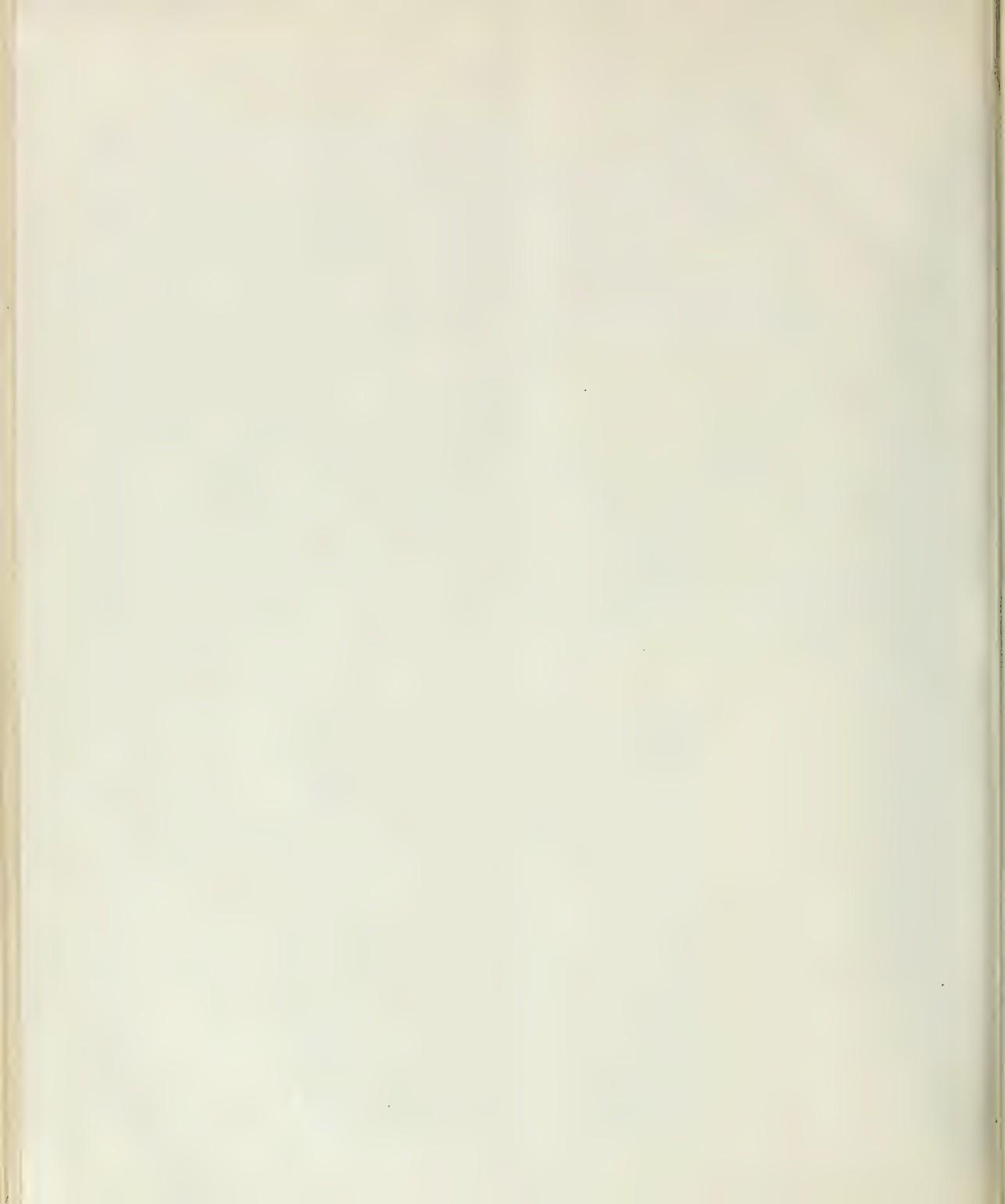
Endocarditis complicating pneumonia has long been recognized. Endocarditis caused by the pneumococcus was discussed by Netter, who in 1886 published a comprehensive review of the literature to that date, including 82 cases. He also reported the results of experiments whereby he was able to produce endocarditis by the intravenous injection of pneumococci, especially after the endocardium had been previously traumatised. He emphasized the point that the pneumococcus involves the right heart one-sixth times as often as the left, whereas other organisms involve the right heart only one-nineteenth times as often as the left. He also confirmed the observation of Heschl that endocarditis following pneumonia is frequently found associated with meningitis.



FIG. 1.—Photograph of the right heart showing the large polypoid vegetation on the tricuspid valve.



FIG. 2.—Photomicrograph of a section taken from the edge of the vegetation, showing gram-positive diplococci. ( $\times 1000$ .)



Osler, in 1885, reported the autopsy findings in 209 acute ulcerative endocarditis cases, 54 of which were in pneumonia patients.

Weichselbaum, in 1888, published a report of an extensive investigation of the pathological anatomy of endocarditis. He reported 29 cases, of which 6 were due to the pneumococcus, as well as describing the lesions produced experimentally in laboratory animals.

In 1890 Debove reported a case of tricuspid endocarditis of pneumococcus origin, emphasizing the absence of physical signs and offering as an explanation for the site of the lesion the lowered resistance of the right heart in pneumonia due to prolonged overwork.

In 1898 James reported two fatal cases of pneumococcus endocarditis in which neither of the patients had suffered from any pulmonary involvement.

In 1902 Wells reviewed the literature and pointed out the fact that acute endocarditis may occur early in the course of the disease (seventh day in one case and ninth day in another). He also stated that recovery from pneumococcus endocarditis was likely to lead to unimpaired function of the valve owing to the slight tendency shown by this type of lesion to the formation of cicatricial contraction.

Preble, in 1904, added 50 cases from the literature to the 82 previously reported by Netter and carefully analyzed the 132 cases. Little of note has been added to the subject since that time. Among his conclusions he stated that endocarditis complicates 1 per cent of all cases of pneumonia and about 5 per cent of the fatal cases. Infarcts occur in about half of the cases. Pneumococcus endocarditis is about twice as common relatively in males as in females. Physical signs of the endocarditis are often entirely lacking. One of Preble's personal cases was the only one, confirmed by a positive blood culture, that recovered, but he thought it probable that a higher percentage of recoveries occur than the reports so far published would lead one to infer.

Of 141 pneumococcus endocarditis cases collected by Preble in which the site of the lesion was indicated, 12, or 8.5 per cent, involved the tricuspid valve alone, whereas 56 and 40 involved the aortic and mitral valves respectively. A careful study of the literature since that time serves only to add five more cases where the lesion was confined to the tricuspid valve; Hawkins two in 1907, Romback one in 1911, and Menétrier two in 1919. With the case reported in this paper that brings the total to 18 cases.

Few cases of pneumococcus endocarditis have been reported since the division of the pneumococcus into its subgroups. In a series of 11 Type I pneumonia cases treated with anti-pneumococcus serum reported by Bloomfield in 1917, one developed acute vegetative endocarditis of the mitral valve.

Mildred Clough, in an analysis of the complications of a series of 36 pneumonia cases, found two instances of acute endocarditis; one caused by a Type III and one by a Type IV pneumococcus. Palmer, in 1919, reported two cases of acute pneumococcus endocarditis of the mitral valve, both caused by the Type I organism. Wadsworth, in 1918, reported pneumo-

coccus endocarditis occurring in horses which were being immunized against living pneumococci. In eight autopsies performed on horses dying during the process of immunization, seven showed lesions of acute endocarditis, five due to a Type I pneumococcus and one each to a Type II and Type III pneumococcus. He stated that the lesions caused by the different type organisms were identical, but it would seem that the preponderance of Type I cases is significant.

In addition to this small group of reported cases there are certain facts which make it seem quite possible that the Type I pneumococcus is responsible for the majority of pneumococcus endocarditis cases, although the proof lies in the accumulation of much more data. In the first place out of 31 cases of pneumococcus empyema, 20, or 60 per cent, were caused by Type I pneumococcus. Out of 49 positive blood cultures 18 were Type I. Of the three infected joints occurring on this service, two were caused by Type I pneumococcus and the other by Type IV pneumococcus. The only case complicated by meningitis was caused by Type I pneumococcus. These facts show the tendency the Type I pneumococcus has to cause secondary infections or complications and to invade the blood stream. In the second place morphologically and culturally Type I pneumococcus is frequently indistinguishable from a streptococcus viridans, which is considered the most common cause of endocarditis. That this cultural likeness is of any importance remains to be shown.

This case suggests the advisability of frequent and early blood cultures during the convalescence from pneumonia whenever a rise in temperature occurs. In a case treated with serum a possible serum sickness should not lead one to neglect this measure, as active serum treatment, while not very promising, is the only procedure at present available with which to combat this condition.

#### SUMMARY.

An unusual case of Type I pneumococcus endocarditis, namely, of the tricuspid valve, is reported. This case brings up several interesting points upon which more statistical data are needed before positive statements can be made. There is, however, some cause for believing that pneumococcus endocarditis is usually caused by the Type I pneumococcus.

NOTE: We wish to express our gratitude to Dr. F. B. Mallory for his co-operation in this report and also to Miss Lillian M. Leavitt for the technical work of preparing the microscopic sections and making the photographs.

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## NOTES ON NEW BOOKS

*Parasites and Parasitosis of the Domestic Animals.* By B. M. UNDERHILL, V. M. D. (New York, 1920, The MacMillan Company.)

This book is not an exhaustive treatise on zoölogy, nor is it intended to be. As the author states in his preface, he has "aimed to present clearly, concisely and in an orderly manner such matter pertaining to the subject at hand as seems most essential to the needs of the student and practitioner." This aim the author has accomplished. The commoner animal parasites and the diseases caused by them in domestic animals are discussed adequately. To the description of most of the diseases there is added a brief note on treatment and suggestions as to their prevention. The illustrations are numerous and clear. Many of them are schematic. This book will be a success as a text-book. In addition to this, because of the interesting way in which the subject matter is presented, it can be recommended as not only profitable but also pleasant reading for any physician, and even probably for laymen interested in domestic animals.

F. A. E.

*A Laboratory Syllabus of Clinical Pathology.* By CHARLES E. SIMON. Cloth \$2. (Lea and Febiger, Philadelphia and New York.)

The author states that the object of this book is to eliminate waste motion in teaching the laboratory side of diagnosis and thus lighten an already overburdened medical curriculum without curtailing the attention given to this important and ever-growing subject. The need for some such measure is acutely felt by everyone with responsibilities similar to those of Dr. Simon, and this guide to his methods from such an experienced teacher in this subject is sure to be appreciated. The subjects for study are wisely chosen and the field is well covered. Many subjects, however, are so briefly presented that one is inclined to question seriously if in actual teaching a sufficient insight would be obtained by the student in the time allotted to them in this syllabus. For example, it would appear impossible to teach the student routine qualitative and quantitative examination of the urine in two two-hour laboratory periods, and microscopic examination in one similar period. One two-hour laboratory period for study of the blood pictures presented by all types of leukemia, and another for all types of anemia are certainly inadequate. Such considerations as these raise the question as to whether a teacher in following this syllabus would succeed in saving time without curtailing the attention given by the student to this fundamental subject. To some who have no more time allotted to them than is outlined in this syllabus it would probably seem wiser to present some parts more fully, rather than cover so much ground thus hastily. The time given to any individual subject, however, may be increased, as Dr. Simon suggests, according to the judgment of the teacher. If this liberty is taken with it, the book will surely afford an outline to follow for those undertaking the teaching of this branch for the first time and as such will be of great value.

F. A. E.

*Infectious Diseases. Practical Text-Book.* By CLAUDE BUCHANAN KER. Cloth \$7. (London, Oxford University Press, 1920.)

From the standpoint of text-books no branch of medicine has been dealt with more inadequately than the infectious diseases. It is a pleasure, therefore, to find a concise and yet sufficiently comprehensive treatise such as that of Dr. Ker. Without going into great detail, or inflicting upon the reader large statistical compilations, the writer presents excellent and vivid clinical descriptions of the various diseases, emphasized by a sufficient number of very satisfactory illustrations.

The book is thoroughly up-to-date, and in the section on etiology prevailing views as to the causes of the various infectious diseases are discussed in a conservative and critical manner.

The sections on treatment are excellent, the questions of diphtheria antitoxin and meningitis serum being handled especially well.

The first and last chapters, dealing respectively with the general questions of infectious diseases and with fever hospital problems, serve to round out the book.

A. L. B.

*Epidemic Encephalitis.* By FREDERICK TILNEY and HUBERT S. HOWE. Cloth \$3.50. (New York: Paul B. Hoeber, 1920.)

The book is divided into two parts. Part I (76 pages) reproduces verbatim the article "Epidemic Encephalitis—A preliminary consideration of some of its prominent clinical and pathological manifestations," by Tilney and Riley in the Neurological Bulletin, Vol. II, No. 3, page 106. This article presents 20 cases illustrating the different clinical types of this disease.

Part II is entitled "Studies of selected cases," and is devoted, in 171 pages, to a presentation of 11 cases, one of which has appeared in a previous publication (Neurological Bulletin, Vol. II, No. 5, page 190). The etiology, pathology, symptoms, laboratory findings, etc., are briefly discussed. The bulk of the book is taken up by detailed case reports which could be greatly abbreviated by the elimination of many negative data. The photographs and photomicrographs are splendidly reproduced.

W. M. H.

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# BULLETIN

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## ON SOME UNPUBLISHED LETTERS OF LAENNEC\*

By W. S. THAYER

One hundred years ago, on or about the 15th of August, 1819, there appeared a book which marked the beginning of an epoch in medical history. One hundred years ago to-day the author was a tired, ill man, seeking a little rest and recreation in his beloved Kerlouarnec near Douarnenez on the coast of Brittany, endeavouring to stay the inroads of a disease which had carried away already his friends Bichat and Bayle, that malady to which he had devoted such brilliant and fertile studies only to fall in the end its victim.

The last two years have brought to me several opportunities to visit some of the scenes of Laennec's boyhood, and through the great kindness of his biographer, Professor Roux and Dr. Cornillot, librarian of the *Bibliothèque de l'Ecole de médecine* in Paris, I have had the opportunity to examine the relics preserved at the museum of the *Ecole de médecine* at Nantes, and to study some of his precious manuscripts.

A few days before my return from Paris last September it was my good fortune to come into possession of the three letters which I take pleasure in showing you.

A word to begin with on the circumstances of his life. René Théophile Hyacinthe Laennec was born at Quimper, in Brittany, on the 17th of February, 1781. 'Tis a charming little town, Quimper, situated at the junction of the rivers Steir and Odet. The town, flanked by a high hill, lies along the banks of the Odet with its rushing tide. The house in which Laennec was born stood on the quay itself. His father, Théophile Marie Laennec, was a notary, a native of Quimper. His mother was an Angevine of noble extraction. The name,<sup>1</sup> Celtic in origin, comes probably from the word "Lenn" which signifies study or reading; it might properly be translated "reader" or "man of study." It is pronounced as if it were spelled "Lenneç"; that is, it *should* so be pronounced. Oddly enough, even in France, it is commonly mispronounced "Laënnec." This is wrong, the diæresis having been added only in recent years by one of his biographers, Théophile Ambroise. None of his family use the diæresis in the spelling of their name, and his collateral descendants pronounce their name "Lenneç."

\* Read before The Johns Hopkins Hospital Medical Society on March 29, 1920.

<sup>1</sup> Saintignon, Dr. Henri: Laennec: Sa vie et son œuvre, 12°. Paris, J. B. Baillière et fils, 1904.

Five years after his birth his mother died, probably of tuberculosis, and Théophile and his younger brother "Michaud" were placed under the care of their uncle, the Curé of Elliant. On the removal of the uncle two years later, the two boys were sent to Nantes, where they were put under the care of another uncle, Dr. Guillaume François Laennec, who, at this time, was rector of the local university.

Laennec's early education was gained at the *Institut Tardivel* and the *Collège de l'oratoire*, which in the school year '91-'92, when Théophile entered, was under the direction of no less a personage than the celebrated Fouché, then a priest. In his uncle William, who was a physician of no mean ability, who had studied with John Hunter in London, Laennec found a devoted friend and adviser, a father indeed, far more of a father than his own brilliant but vain and scatter-brained parent. Some of the talents and tendencies of this parent he inherited and manifested early in his career, to the considerable discomfiture of his uncle; such for instance as a remarkable facility in versification.

In 1795 he began to study medicine at the Hôtel-Dieu de Nantes. At the same time he was an ardent student of the classics. At the age of 11 he translated the first eclogue of Virgil into excellent French verse. He was especially interested in Greek. While devoted to out-door sports and to natural history, the boy, rather early, became impressed with the desirability of perfecting himself in a variety of arts and graces which might fit him better to commune with the great world. He desired earnestly to take lessons in dancing. He felt that he should learn how to play some musical instrument and, indeed, became a flute player. He could not help playing the flute. No one with an upper lip like his could fail to play the flute.

In 1798 a severe continued fever, probably typhoid, nearly cut short his career.

In 1800 he accompanied the forces of General Grigny as an army surgeon during the campaign in le Morbihan, passing his time principally at Vannes and Redon. During this campaign he wrote an amusing poem entitled "La guerre des Venètes" which purported to be a translation of the work of an old Celtic bard, Cardoe, by a Breton of the name of "Cen-neal"—obviously his own name reversed. The manuscript of this interesting production which his father had, or sought to have done into Celtic, was lost for a number of years. It has recently been found and is now in the possession of Professor Rouxéau.

For several years it looked as if the improvident parent might fail to produce the wherewithal to send his brilliant son to Paris, but finally, in 1801 Laennec entered the *Collège spécial de santé*. There he devoted himself especially to study in the clinic of Corvisart at the *Charité*, then known as the *Unité*. He became a companion of the brilliant Bayle, with whom he began important anatomical and pathological studies under Dupuytren. This early anatomical work, normal and pathological, was notable. He was the first to describe the subdeltoid bursa, as well as the fibrous capsule of the liver. At the age of 21, in a remarkable communication, the result of the

analysis of six cases with necropsies, he set forth the first clear clinical and anatomical picture of peritonitis. For general peritonitis Laennec did that which, some 80 odd years later, Fitz did for appendicitis.

At the same time his brother Michaud, who was preparing for the law, was gaining new laurels. In 1802 this brilliant boy entered three contests at the *Ecole des quatre nations*, taking the first prize in all—French, Latin literature and general grammar. In the following year Théophile, in the *Concours des Ecoles spéciales de Paris*, took the first prize in medicine and surgery. He was bitterly disappointed in missing like honours in chemistry and anatomy. The reputation of the brothers had, however, become so formidable that when at the next concours of the *Ecole pratique*, his name was entered, there were no contestants, and at the request of his instructors, he withdrew from the contest.

In 1804 Laennec published a remarkable article on "Vers vésiculaires." Some of his original drawings for this publication I saw last summer at Nantes. He cannot be said to have been an artist, but the work was carefully and well done.

In the same year he published his thesis, "Propositions sur la doctrine d'Hippocrate relativement à la médecine." The thesis contains much that is interesting and sound. Here is a paragraph:

The only method by which one can acquire solid knowledge in medicine depends on avoiding the adoption of any principle which is not proven by many individual facts; by studying with care the character and course of diseases and by treating them according to the indications drawn from the observation of that which has succeeded in like cases. This is the method which Hippocrates asserts to have been known long before him, which he presents as the only way by which one may make real discoveries.

In the same year he became a member of the *Société de l'Ecole de médecine*, the precursor of the *Académie de médecine*. He was likewise made an editor of the *Journal de médecine*.

In 1805 he published a valuable article on the classification of organic changes; this led to a distressing quarrel with Dupuytren, which lasted for several years. He was feverishly active, working day and night. Delicate, rather frail physically, he was very fond of out-door sport for which, alas, he had small opportunity, and his uninterrupted studies told upon his health. The happy presence of a cousin, Madame de Pompréy, at the *Château de Courelles*, near Soissons, afforded him the opportunity for a much needed vacation. Rouxéau, in his biography,<sup>2</sup> gives a charming account of his visit, during which he met the young woman who was later to be his wife. This account bears interesting testimony to his social charms and to the ease with which he wrote really rather clever verse.

In 1812 he was made *médecin suppléant* at the Beaujon. In 1814 he was attending physician at the *Salpêtrière* which was then a military hospital. In 1805 he had taken up the study of the native tongue of his people and had acquired a reading and speaking knowledge of the Celtic dialect of lower Brittany.

<sup>2</sup> Rouxéau, Alfred: Laennec avant 1806, 8°. Paris, Bailliére et fils, 1912.

In 1814 there were, in the Salpêtrière, many young Breton conscripts, wholly unable to speak French and wretchedly home-sick. To these poor fellows Laennec was a God-send. "More than one," says Rouxau,<sup>3</sup> ". . . doubtless owed his recovery to the joy of finding in Paris a compatriot who knew so well how to comfort them in their maternal tongue."

In 1816 he became chief of service in the Hôpital Necker. It was in this year that he made his famous discovery of the stethoscope. The story has been told so often that one need not repeat it here. With the introduction of the stethoscope and the revelations following its use, he began immediately to accumulate the material which later formed his book. Under the strain of his increasing practice and his constant and engrossing studies, his health began seriously to give way, and in August, 1818, he took a vacation of several months in Brittany, whence he returned on the 1st of November. While correcting the proof of his book, he was at the same time busy with the manufacture of his stethoscopes. Professor Rouxau tells me that it is probably true that all the stethoscopes in existence at the time of his death were made by Laennec himself. Working with a lathe in his own room, he sought to prepare enough instruments so that whosoever bought the book might have a suitable implement with which to pursue his studies.

In these days of prolific terminology, when so many of us coin with delight strange, new, and often barbarous words to express simple things, it is interesting to know that Laennec, who wrote and spoke clearly and simply himself, resisted the introduction of any term for the instrument beyond the simple word "cylinder." Others, however, sought to name the implement for him, and in the end, somewhat reluctantly, he gave way, modifying the term "thoraciscope," suggested by his uncle Guillaume Laennec, by substituting the other Greek root.<sup>4</sup>

About August 15 the book finally appeared, marking, as Rist<sup>5</sup> has well pointed out, the beginning of modern clinical medicine.

But in its precious folds were imprisoned the heart's blood of its author, and on the 16th of August he writes to his colleague Pérusel of his suffering, his "*hypochondrie, goutte, asthme*" and says: "I am determined to abandon medicine and Paris and retire to Brittany, where few patients, I hope, will be tempted to seek me." At the end of the year, exhausted and suffering from that "asthma" which but too clearly must have been the beginning of his fatal illness, he retired to Kerlouarnec where he spent two years in rest and recuperation.

But he could not resist the call of life and activity in the capital. Health, or the semblance of health returned, and early in 1822, he reappeared in Paris to find himself appointed physician to the Duchesse de Berri, an honorable post but not a sinecure. He was soon made professor of medicine at the *Collège de France*. His practice became arduous. His lectures at the university were carefully prepared and revised, as is testified to by the notes which remain. The first of these,

delivered on the 22d of August, 1822, forms the introduction to the *Archives générales de médecine*.

At that time Broussais, with his doctrine of irritation, held full sway. With him the clear-seeing Laennec could not fail to clash. Impetuous, ardent, dogmatic, eloquent, Broussais had a large and enthusiastic following, and the controversy between the two professors was celebrated. It is interesting to-day to read the fine, impassive, logical comments of Laennec upon the views of his fantastic adversary. While Broussais captured the popular imagination and had a large following, the real ability of Laennec soon made itself felt among the more thoughtful students. His clinic grew in popularity; his name became more widely known, but his health could not long stand the strain.

In 1824 he married Madame Guichard-Guéguen, veuve Argou, his devoted companion and house-keeper for many years. He was made a Knight of the Legion of Honour. Already in 1824 the first edition of his book had given out. With the new material that he had collected, Laennec had been busily engaged on a second edition in which the original book was almost rewritten. By May of 1826 the revision was finished, but its preparation had exhausted the physical capital of its author. At the end of June, he gave up his work in Paris and returned to Kerlouarnec, where he died on August 14 at the age of 45.

It was a life of great achievement. He had made important contributions to anatomy; he had taken his place among the great pathological anatomists. He had been the first, anatomically and clinically, to describe peritonitis, bronchitis, emphysema, pulmonary oedema, pulmonary apoplexy. He was the first accurately to describe the character of the sputa in pneumonia, and his pictures, anatomical and clinical, of pneumonia and of pulmonary tuberculosis will always remain classics. His methods of clinical study have never been surpassed, and stand a model for the clinician of to-day. He might almost be called the father of modern clinical medicine. For with all the work of Auenbrugger and Corvisart, the art of physical diagnosis hardly existed before Laennec.

Personally he was a small, rather delicate looking man, with curly chestnut hair. The face was rather thin and oval with a particularly long, typically Celtic upper lip, which is striking in the bust of Toulmouche at Nantes. Last summer, through the courtesy of Professor Rouxau, I had the happy chance of seeing not only this bust, but also the one good portrait of Laennec which exists. This portrait, painted by Dubois in 1812, is owned by his great-nephew M. Robert Laennec, who most graciously received us at his charming place in the suburbs of Nantes. The picture is life-like; one feels that it must have been a good portrait. The face and figure are most interesting. The expression, somewhat *narquois*, is attractive—a fine, witty, rather whimsical look. Although the man seems small and thin and delicate, yet the long, pointed, typically Irish upper lip and something about the mouth give a strong suggestion of vigour and spirit and humour. One can well fancy his physical energy. 'Tis a striking painting of an engaging figure.

The three letters which follow were written to an old school

<sup>3</sup> *Op. cit.*

<sup>4</sup> Rouxau: *Paris méd.*, 1919, XX, No. 44, III.

<sup>5</sup> Rist, E.: *Presse méd.*, Par., 1913, XXI, 357.

mate, Dr. Courbon Pérusel, of Carhaix, in Finisterre, who has consulted him because of a "d'artre," a term which, in those days, evidently covered a large variety of cutaneous manifestations from simple seborrhœa and senile keratosis to graver affections. 'Tis clear from the context that the good fellow's annoyance was based largely on moral compunctions as to the justification of his contemplated matrimony. Laennec endeavours to reassure him, and upbraids him for what he considers purely hypochondriacal fancies. But it is three years before Pérusel is convinced; and before he can persuade himself that he is justified in taking the momentous step, he has consulted the fashionable dermatologist of the day, Jean Louis Alibert, with regard to whose methods Laennec expresses himself with some severity.



BUST OF LAENNEC BY TOULMOUCHE (1844), TAKEN FROM PARIS MÉDICAL, NOVEMBER, 1919.

The first letter was begun on the 22d of April, 1817, and the first folio, in which Laennec gives so vivid a description of his busy life, is written evidently at one sitting, one might fancy before going to bed. The next four pages are written on separate sheets. The fourth page ends with the words: "Je crois qu'en—." The fifth page continues the sentence, "somme, on ne doit," etc., but is written with another pen and in a somewhat different form, clearly at another time. The sentence is finished, however, before the confession which follows in two lines, in the shape of a new date "29 Avril," and an acknowledgment that there has been a week's interruption in the letter. How many of us have done the same!

The second letter in which he speaks of his intention to retire to Brittany, is written on the 16th of August, 1819, the very day after the publication of his book. The third, fourth, fifth, sixth and seventh lines are in great part erased, "scratched out," the erasures apparently made by his own pen. By careful study with a lens it has, however, been possible to discover the original text. The same is true of his later reference to Alibert. The several words erased in the thirteenth line of the second letter I have not been able to read.

Paris 22 avril 1817.

J'vous demande mille pardons, mon cher docteur,  
d'avoir tant tardé à répondre au vostre letter du 28  
fevrier que j'ai reçue le 9 mars. Depuis ce jour il n'en  
est pas passé un, sans que je me proposasse de vous  
écrire le lendemain. Je vous dois des excuses gênantes  
et évidentes, car je suis honnête. J'avais été tout le  
soir en arrêt chez moi, et au conséquens  
je vais vous expliquer tout en détail comment il  
se fait que le plus grand désir de savoir des  
nouvelles de mes amis et même de leur mariage  
fond presque toujours par ce leur jalousie évidente que  
dans les cas de la plus urgente nécessité. Je faire  
pour cela vous expliquer mon genre de vie. Je  
me lève à 7 h<sup>o</sup> ou même 6 h<sup>o</sup> car j'ai besoin de  
beaucoup de sommeil. Je habite depuis souvent un  
donnant des consultations. Je vais faire une visite  
à l'hôpital (l'Hôpital Neuf) il revient un bout de  
clinique aux élèves qui le suivent, cela me prend à 10 h<sup>o</sup>  
et déjà le temps me presse assez pour que les deux  
réunissent que je puisse pas recevoir leur ami pour  
déjeuner; je commence donc une tournée qui  
se finit que vers 5 h<sup>o</sup>, après dîner, est à dire vers  
6 h<sup>o</sup>; j'en reviens une autre jusqu'à 10 h. Il me  
reste ensuite une heure jusqu'à 11 h que je me couche  
quelques minutes et de temps en temps  
avant le déjeuner et le dîner, pour venir à jour  
mes correspondances de toute espèce, corriger et éditer  
ou ordre les observations recueillies par les élèves dans mon  
hôpital, régler mes petites affaires etc. Ainsi cette  
peuvent me donner qu'il faille idée de ce qu'est  
pour un homme en peu occupé, que le tourbillon  
~~affection~~ de relations de toute espèce dans lequel on  
se trouve emporté à Paris, quelques fois qu'on vailler à  
les empêcher. J'ai souvent été étonné que vous et  
quelques autres de nos compères vous foyez retenu  
chez de très-petites villes, aujourd'hui je vous leus  
et approuve très-fort et je loue vos mœurs honorables  
(entre nous) à arranger vos affaires de manière à  
pouvoir vous très-peu demander une retour en bâche lorsque  
j'avais ce qui meut dès ici, alors ce serait grande  
des agacardes.

Je viens à la question sur laquelle vous me  
consultez. Je ne conçois pas que vous pourriez  
la délicatesse à une guérison extrême. La contagion  
des d'artres dans les plus graves malades, est  
assez-souvent très-obscure; je ne sais si l'application  
immédiate et continue produisant quelque temps  
d'un d'artre phlegme d'origine en ~~appareil~~  
apparition produirait autre effet que celui  
d'un rebouffant, mais je fais bon nombre de  
malades qui ont des d'artres incurables avec  
certaines sans avoir jamais rien communiqué  
à leurs familles et vice versa. Quant aux d'artres  
torseaux comme les vôtres, un bon tiers des  
gens humains est attaqué à une époque quelconque  
de la vie, et après 60 ans, il n'y a qu'une d'individus  
sur ce quels on n'en trouvait en élaborant bien le  
peau de l'humilité de la peau à cet âge fait qu'on les

\* The letters are reduced to one-half their original size.

pose le plus souvent sans son doute.

Si l'on s'en rapportait à l'opinion de la plupart des barbouins et hérétiques des dernières, ils auraient contracté tous cette affection par contagion : mais en observant avec une peu d'attention, on voit que tous le rapport de caractères propres de l'affection des d'herétiques et appartenant par des nuances insensibles à d'autres affectés dans lesquelles on ne s'est jamais avisé de supposer la contagion et particulièrement de certaines variétés de l'hydrocephale à marche chronique. 2° que tous le rapport est logique, pour un cas où l'on pourrait supposer la contagion), on en voit des milliers qui prouvent le contraire ; que chez un très grand nombre d'individus, les d'herétiques sont le produit d'un mauvais régime et particulièrement de la misère, de la mal propreté, des veilles trop habituées, des usages d'étude des exercices de table, de l'inspiration habituelle du froid ou de l'humidité (humidité, orages, averses) et en général de toute les causes qui dérangent la transpiration insensible, ou les malades réellement et absolument contagieux, tels que la peste, la pelle virale, la typhoïde contagieuse, la syphilis ne se produisent pas (cas évidents de régimes). on peut même appeler contagieuses tout ce qui circule et circulerait, les malades dues à des exercices analogues qui se propagent le plus rapidement, comme le typhus des camps et hospitaux ; car quelques-uns qui ont dit pour établir l'existence de la contagion dans ces cas, on a procédé seulement quelques très nombreux récidsives d'herétiques malades dans un lieu trop étroit fait exactement pour l'infection (ce qui est tout ce qu'il convient d'admettre si on veut bien aborder sans y entrer) une fièvre grave à laquelle on a vainement cherché des caractères propres, car ils varient dans chaque opération. Separer les malades, donner à chacun d'eux de l'aspirine et des tonics de préférence à la pâte de la peste, qui obéiraient à proposer un garde réellement contre la peste et la grippe ?

(pour revenir) aux d'artres, et une malice que les  
faits démontrent que presque tous les hommes y  
ont disposé plus ou moins; que beaucoup d'entre eux  
sont de paroles non d'artres ce sont affaires des  
leur bas âge (deux ou trois ans); que d'autre  
sont en entretien avec diverses personnes de la race  
par suite d'erreurs hygiéniques, et que la ville  
n'est pas, à elle seule, susceptible de contracter le contagie  
en aucun cas, de gens qui n'en avaient  
jamais eu. je pense ~~que~~ que quand il  
les regarder ~~que~~ quand ils sont à nos  
deux amis (et qu'elles ne sont pas dues à des  
causes aussi évidentes, comme une simple insensibilité  
qui résulte d'un état d'équilibre dans une constitution  
si élevée très-bonne). ~~que~~ que j'les voyais nus, un  
le rapport aux sondes qui lorsqu'elles existent  
des deux sujets (un très-léger degré chez) des  
sujets si élevés l'air et robustes ne sont-elle-mêmes  
que l'air d'une constitution élevée la meilleure  
de toutes; le tempérament lymphatique sangine,  
et se sont apprises que pour les médecins, les d'artres  
se sont vaincu avec les serpules chez des enfants  
en 2<sup>e</sup> et 3<sup>e</sup> années excepté de ces affections: mais l'une et  
l'autre ~~qui~~ communiquent quelquefois par l'ingestion  
~~qui~~ comme la constitution même des garçons  
nous n'avons à leur tour de vain. je crois qu'en

Somme, on ne doit les regarder comme une maladie à traiter que quand elles sont très-fortes.

29 avril j'avais date<sup>re</sup> ma lettre du 22  
courant envoient l'auant-termeine ce jour là.  
vous vous à la fin d'auoir et jo n'a<sup>veu</sup> encore que  
terminer cette<sup>e</sup> lettre écrive comme tout ce que  
j'peux, à l'atours rouge. il faut pourtant  
que vous ne l'attendez pas d'avantage la  
date en écrité n'invalide pas la peine et  
je vais le tresseriner en vous disant de ces  
mots de ce qui en a le mieux résoffice et fait  
de tractement.

à dos aussi forte et je fais même à deux ouees  
j'obtiens une production d'environ 7 kg par individu des œufs  
jaunes lorsque leur côté de l'ouverture avec distorsion  
de la coquille qui est précisément alors créée que  
les œufs peuvent un peu de temps dans une baignoire  
et accidentllement en train ou le jours en interrompant  
le renouvellement.

De tous ces dégagements, celui qui a le mieux réussi, c'est l'usage des bains sulfureux préparés avec trois onces de sulfate de potassium solide pour un bain auquel on ajoute en outre une douzaine de verres d'eau minérale ou le gros de deux kilogrammes dans notre cas, je me contente de prendre une vingtaine de ces bains au moins de ceux-ci, suivant en faire, et alors je prends dix ou quinze minutes qu'il faut faire pendant que je prendrai un autre pendant un quart d'heure long, deux verres d'eau sulfureuse remplissant l'heure avant chaque repas suivant la première servante

2<sup>e</sup>. pays de surface solide  
pure)

*Scare* ~~Scare~~ *Scare* *Scare* *Scare* *Scare*

- d' autres fonder sans  
- un autre endroit

see ~~the~~ clouds to  
wetter and wetter

Wetter am Sonntags  
Kinder sind die

is deliver'd you dra

*purpureo-virens*

parte dos contínuos. Nis-

L'usage de la liqueur pulparum ci-dessous  
meut d'après ce que j'ai obtenu depuis de  
beus & de nos succès, si parallèle boute  
le verrait-mais je préférerais les beus  
Si quelque boute se trouvait sur une  
partie d'où il fait bon de la déplacer  
le plus tôt possible, comme la figure, le  
bain de la boute, & je vous conseillerais de  
la toucher légèrement avec la gousse  
infusale; ~~à la~~ c'est la précision qui empêche  
en fait que changer la nature de l'infu-  
sation, est sans inconvénient. J'ai vu ici  
un malade âgé de 80 ans, qui a été guéri  
à 86 de boutees étendues par l'usage  
de l'huile de lait par l'apothicaire  
qui était étendue avec une gousse de la  
Vitellion. cela coûtait d'abord avec  
3/4 d'eau et on fit par l'empilage  
jusqu'à la fin de l'infusion employé un  
peu temps équivaut à rien, mais  
avoir le temps de se donner d'avantage,  
mais intelligible, mais

j'ai fait dans le temps des démonstrations  
pour lui & votre frère, mais j'osais é-  
voquer que l'atténuation sera principalement  
pas un titre de recommandation auprès  
de bien des gens, et rien n'a changé, l'usage

ici à cet égard.

J'ai été bien fait de n'avoir pas 3 ou  
4 jours à moi long-jeudi à guérir par 1813.  
~~—~~ Je suis proposé d'y aller faire un tour  
l'année prochaine et cette fois j'ajourrai bien  
que pourrais m'arranger de renouveler à vous  
votre visite. J. vous embrasse de tout mon cœur

Votre amitié et aussi  
M. Lacoste des

Monsieur C. M. S.  
Doutre en Médecine à  
Carhaix Finistere

Paris 16 aout 1819.

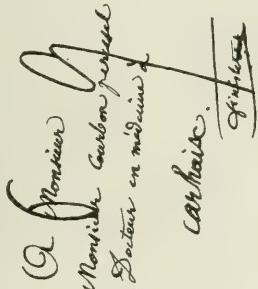
je ne conçois pas, mon cher frère, vos inquiétudes  
sur le fond et les circonstances des très-légères incommodités  
que vous éprouvez. Pour ces légères incommodités  
vous pouvez assurer que tout est dans l'ordre au point de la santé  
de la partie, du système; le tout que nous avons  
determiné à redoubler nos soins des et faire et à  
ne retirer au Bretagne où que de malades, je l'espère,  
seront tentés de faire une relâche, je pars d'ici vers 6h  
du matin et probablement j'aurai le plaisir de vous voir en  
fin car une petite affaire me conduira à Marseille et je  
passerai certainement en allant ou revenant par ce port.  
Nous pourrons alors causer à loisir ~~à Paris~~.

La votre place je me bornerais à prendre tous  
les ans un trajet de boutees pulparum aux printemps  
et surtout en automne pour atténuer les boutees & je  
ne chercherai pas à venir de barrasser tout à fait de  
peur de pris, quant à la crainte de la contagion  
je suis réellement ~~sensibilisé~~ (médicalement parlant)  
que alors vous trottez encore dans le pays, en bonne  
conscience, si j'avais une fille ou une sœur à marier  
vous étiez de m'empêcher ou volontiers de vous la  
donner. Les boutees, les rhumatismes, la phthisie, et boutees  
d'autres maladies ne sont toutes connues être contagieuses  
que parmi elles sont très-communes, et au contraire  
elles des fèces détruit facilement à leur pique.

J'ai communiqué votre message à M. le docteur  
~~de la ville de Paris~~, ~~qui a été nommé à la tête de l'Institut~~,  
je lui ai dit qu'il l'agréait. Il a confirmé ainsi de faire  
l'avantage son attention et sa connaissance j'eusse  
envie de votre vérité. Vous verrez que ma prescrite  
n'a pas servi à grand chose: car il n'eust à ~~compter~~  
comme à un autre une formule banale de conti-  
nuation, ou vous trouverez ~~ce que vous savez aussi~~

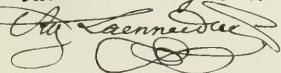
Réécrit par Douarnenez 38 Janvier  
1820

Bien que l'an et presque une idée dont vous plusieurs fois m'avez parlé, comme si l'on ne pouvait prendre de bonnes salpaires qu'à Paris, oubliant laquelle il s'agit à un médecine. Auparavant il a parut assez plus difficile à carbuncle que dans les deux dernières années. Dans ces baignets il aimes de faire de souffrir et au dessus d'eux d'aspirer, et si l'on peut faire des bouches à l'oreille, il est alors difficile mais plus de faire faire un baignet de fer-blanc et de l'adoucir au bout d'uroboros pour servir de l'eau de greve (ce) stage auquel il a été échappé. Il a été bien dans ces préparations extrinsèques à laquelle lui n'a pas été échappé mes yeux, je les garderai toutefois différemment constitutives légères et expérimentées. Il a adopté cette pratique et le fait parfois à ce stade de la guérison inférieure, et en effet dans la position, il est connue de guérir promptement le Dardier, ne fait ce que pour un temps, cela lui donne le vague surtout auprès des larmes, et comme il se voit moins que des étrangères valeurs à parer pour la partie brûlante, il ne voit guère les suites. Il fait connoir d'ailleurs que

  
 Dr. Monin Carbonneau  
 Docteur en médecine

Toutefois de ces constittives des raccourcissement des inconvénients graves  
 mais apparemment nous n'aurons pas assez d'expériences pour faire à ce  
 que l'on voit autour de la peau à quelques grains que ce soit, comme  
 à l'infirmité de la peau.

Votre tout dévoué confrère et ami

  
 Dr. Lacomme

By means of the lens it has been possible to decipher the third, fourth, fifth, sixth and seventh lines which have been in great part erased, as well as the reference to Alibert in the seventh line from the bottom of the page. These lines should read as follows:

"pour moi, je me bornerais volontiers à n'en pas avoir d'autres. il est vrai que j'en ai tout autant que vous, ou peu s'en faut, et de plus, de l'hypochondrie, de la goutte, de l'asthme; tant y-a-t'il que je suis déterminé à abandonner la médecine = "

The seventh line from the bottom of the page should read: "comme il est toujours aussi léger que vous l'avez connu."

j'ai reçu en ton temps, mon cher parent, toutes lettres des mois derniers, à laquelle la vie errante que je mène ici pendant que l'on rebâtit à peu près en entier mon horizontage, m'a empêché de répondre pleinement.

J'ai appris par Toulaït notre mariage, et je vous en félicite d'autant plus sincèrement que je sais que vous êtes honnés à apprécier toutes choses de leur valeur véritable, ce qu'on ne peut pas dire de tous les gens qui se marient. Il en est une circonstance à laquelle vous donner, à mon avis, beaucoup trop d'importance; c'est le cas de médecine dont vous me parlez. Je ne puis vous blamer davantage que le conseil d'Alibert (qui ne fut pas) vous pouvoit être sûr qu'il l'a donné aussi légèrement que lorsque tout ce qu'il donna au public; mais

je crois que vous faire bien de vous en tenir là pour le moment et surtout d'être resté sur l'usage des dépuratifs minéraux. Vous savez comme moi que le long usagedu soufre dit certainement quelquefois des crachements de sang, et vous connaissez tout aussi bien les inconveniens d'un gout différent des préparations d'hydrogypse.

optima iatrdium medicina, medicina non agere. Je ferais pour vous  
 conseillé et pour aller d'autre (quand je trouve les gens assez sage) cette  
 maxime de celles, dans toutes les  
 petits malades qui sont beaucoup  
 plus difficiles à guérir qu'à  
 supporter, et je vous conseille au  
 aussi d'en faire autant.

J'rai au baignet, vous souvenez  
 à ce sujet, comme je vous l'ai  
 promis et j'espère que ce sera

*Dans le courant des prioritaires  
en attendant recever l'approbation  
Dubois finira et achèvera de  
Notre tout dévoué confidante  
au Dr A. Kennedy*

First letter written to,

M. Courbon Pérusel,  
Doctor of Medicine at,  
Carhaix, Finistere,

PARIS, 22 April, 1817.

I beg a thousand pardons, my dear Pérusel, for having so long delayed in answering your letter of the 28th of February, which I received on the 8th of March. Ever since that day not one has passed without my having intended to write to you on the following day. I owe you full and entire apologies, for I am ashamed to have been so often in arrears to you, and consequently I am going to explain to you in detail how it comes about that with the greatest desire to learn all the news of my friends and even to write to them, I end almost always by writing to them only in the case of the most urgent necessity. In order to do this I must explain to you my manner of life. I rise at half past seven or even at eight o'clock, for I need much sleep. I dress myself, generally, while giving consultations. I make my hospital visit (at *l'hôpital Nécker*) and then a bit of clinic to the students who follow me. This brings me to half past ten, and already time presses me to such an extent that generally I cannot return to my house for luncheon. Then I begin a round of visits which ends only at about half past five. After dinner, that is to say at about half past six, I begin another round which lasts till ten o'clock. There then remains for me one hour until eleven when I go to bed, plus several minutes from time to time before breakfast and dinner to keep up-to-date my correspondence of all sorts, to correct and put in order the observations gathered by the students in my hospital, to arrange my little affairs, and so forth. This picture gives you but a feeble idea of that which, for a man who is rather busy, is this whirlwind of relations of all sorts in which one finds himself carried away in Paris, however hard one tries to simplify them. I have often been astonished that you and some others of our confrères should have retired to very small towns. To-day I applaud you and approve very strongly. For myself I think very seriously (*entre nous*) of arranging my affairs so as to be able, in a very few years, to retire to lower Brittany. Had I that which was due me here it would probably be to-day.

I come to the question on which you have consulted me. I can not see how you can push your delicacy to such an extremity. The contagious nature of *dartres* in the gravest cases is certainly very obscure. I know not if the immediate and continued application during a period of time of a phagedenic *dartre* in full suppuration could produce an effect other than that of a rubefacient, but I know a good number of husbands who have exudative *dartres* on the scrotum without having communicated anything to their wives, and *vice versa*. As for furfuraceous *dartres* like yours, a good third of the human race is attacked at one period or another of their lives, and after 60 years there are no individuals on whom one may not find them if one search well. The slight sensitiveness of the skin at this age brings it about that people have them generally without suspecting it.

If one were to turn to the opinion of the greater part of the men and especially the women affected with *dartres* they would have it that they had all contracted the affection by contagion, but on

observing with a little care, one sees, 1°, that considering the essential nature of the affection *dartres* approach by insensible nuances other cutaneous diseases of which we have never thought of suspecting the contagiousness, and particularly certain varieties of erysipelas of a chronic course. 2°, that from an aetiological standpoint, for one case in which one might suspect contagion one sees thousands which prove the contrary; that in a great number of individuals *dartres* are the product of a bad régime and particularly of want, of uncleanliness, of too habitual loss of sleep, of excesses in study, of excesses of the table, of habitual exposure to cold or humidity (in certain workmen) and, in general, of all those causes which disturb the insensible perspiration. But the diseases really *et absque dubio* contagious, e. g., plague, smallpox, contagious itch, syphilis, do not arise from transgressions of régime. One should not call *contagious*, but epidemic and endemic those diseases due to analogous errors which spread most rapidly, such as typhus of camps and hospitals; for whatever has been said to establish the existence of contagion in these cases, it has been proved only that a reunion of too many healthy or diseased men in too restricted an area gives rise to a centre of infection which one may not frequent or sometimes even approach, without contracting there a grave fever for which one has vainly sought specific characteristics, for they vary in each epidemic. Separate the patients, give each one of them space and attention as to cleanliness, and the supposed contagion ceases. Who would dare to propose a like remedy against plague and smallpox?

To return to *dartres*, it seems to me that the facts show that almost all men are more or less subject to them; that many children born of non-dartrous parents are affected with them in their early age (the same is true of scrofula); that others contract them at various periods of their life as the result of hygienic errors, and that old age, the age least susceptible to contagious diseases, brings them to many people who never had them. I think that when they are of moderate degree and not due to accidental causes, one should regard them as simple commodities, the result of a loss of equilibrium in a constitution in other respects very good. I should compare them from this point of view to scrofula, which when it exists to a slight degree in a subject in other respects healthy and robust, is really not more than the excess of a constitution which is indeed the best of all, the lymphatico-sanguine temperament, and is recognized only by the physician. *Dartres* arise as does scrofula in infants born of parents free from these affections. But both of these diseases are communicated sometimes by generation as is the very constitution of the parent, their physiognomy and the sound of their voice. I think that<sup>\*</sup> on the whole one should not regard them as a disease to *treat* excepting when they are very severe. 29 April—I had dated my letter the 22d current hoping to have finished it on that day. Here we are at the end of the month and I have not yet been able to finish this letter written, as is everything that I do, in broken periods. You must not, however, wait for it longer. The affair, indeed, is not worth the trouble, and I am going to finish by saying two words to you concerning that which has given me the greatest success from a point of view of treatment.

I have never accomplished any appreciable effect with *scabiosa*, with *fumaria*, with the root of wild pansies (which I have employed but little), with preparations of antimony. Anti-scorbutics have seemed to me to have some value in scrofulous *dartres*, sublimate in cases in which one may fancy a syphilitic base. I have had remarkable success with bitter almond in two or three cases of scaly *dartres* of great intensity: but in a multitude of other cases, I have obtained no results, although pushed gradually

<sup>\*</sup> Here ends the fourth page of the manuscript. The continuation on a new sheet is written with a different pen and clearly at a later date.

to a dose of *3 to 4 ounces* for three glasses of decoction, which the patient took each day and continued during eighteen months and more thereafter. At a dose so large as this and sometimes even of two ounces I have seen it produce in some individuals a tonic spasm of one side of the face, with distortion of the mouth and embarrassment of speech, which at first glance might have been taken for a sign of hemiplegia. This accident ceases in three or four days on interrupting the remedy.

Of all the depuratives that which has given me the best results is the use of sulphuric baths prepared with three ounces of solid sulphate of potassium for a bath, to which is added besides, a half glass of vinegar or four drachms of sulphuric acid. In your case I should content myself with taking twenty of these baths in the month of May, as many in September, and this for several years if it should be necessary. And I should take in addition for a longer time, that is say 3 or 4 months, a glass of sulphurous water a quarter of an hour before each repast according to the following formula:

R Solid sublimed sulphur.....	3 i
Sugar .....	3 iv
Dissolve in hot water.....	0 ii
Put in bottle, cork and allow to cool.	

I freed myself ten years ago of two furfuraceous, scaly *dartres* by bitter almond in large doses continued eight months and the use of the above sulphurous fluid. But from the successes and the non-successes, if indeed I have had these, which I have obtained since then, I should prefer the baths.

If a *dartre* should exist in a region where it were well to remove it so soon as possible, on the face or at the corner of the mouth, etc., I should advise you to touch it lightly with nitrate of silver; this procedure which at the bottom, but changes the nature of the inflammation is without inconvenience. I have used it upon myself. I have seen here a patient of 80 who was cured at 56 of extensive *dartres* by the use of deliquescent oil of tartar ("par défaillance") which was painted upon the eruption with a brush. It was first diluted with three-fourths water and in the end employed pure. The internal treatment employed at the same time was of no significance. I wish I had the time to go into the matter more extensively, but *intelligenti pauca*.

I have taken some steps recently to assist (?) your brother. But I had occasion to observe that attachment to "*principes*"<sup>1</sup> was not a title of recommendation with many people and nothing has yet changed here in this respect.

I was much vexed not to have three or four days to myself when I was in Quimper in 1814. I propose to go there on a trip the coming year and I hope sincerely that this time I may arrange to be able to visit you. I embrace you with all my heart.

Your confrère and friend,  
R. T. H. LAENNEC, D. M.

Second letter, written to,

M. Courbon Pérusel,  
Doctor of Medicine at,  
Carhaix, Finisterre,

PARIS, 16 August, 1819.

I can not conceive, my dear Pérusel, your anxieties as to the essence and the circumstances of the very trivial inconveniences from which you are suffering. (So far as I go I should be well content to have nothing more. It is true that I have fully as many as you, or approximately, and in addition hypochondriasis, gout, asthma, and so forth; so much, indeed that I am determined to abandon medicine)<sup>2</sup> and Paris and to retire to Brittany where

<sup>1</sup> Underscored in the original. Are we, perhaps, to accept the word in its Latin sense?

<sup>2</sup> These lines are erased by heavy marks of his pen.

few patients I hope, will be tempted to seek me out. I am leaving on about the 16th of September and probably I shall have the pleasure of seeing you in October, for a small affair will bring me to Morlaix and I shall certainly pass through Carhaix in going or returning. We can then speak at leisure.<sup>3</sup>

In your place I should restrict myself to taking yearly thirty sulphurous baths in the springtime and as many in the autumn to attenuate the *dartres*, and I should not endeavour to free myself entirely for fear of making things worse. As to the fear of contagion I am really *scandalized* (medically speaking) that such an idea still runs in your head. On my conscience, if I had a daughter or a sister to marry, your condition would hinder me in no way from giving her to you. *Dartres*, scrofula, phthisis, and many other diseases are suspected of being contagious only because they are very common, and a careful examination of the facts destroys this suspicion very easily.

I have communicated your memorandum to Alibert. (As he is always as frivolous as you have found him)<sup>4</sup> I told him that it was the question of a colleague in order better to fix his attention, and as a result I am sending you your prescription. You will see that my precautions have not been of great service: for he has given you, as he would to another, a common formula of consultation, where you will find that which you know as well as he and not an idea from which you may profit. You will see that he talks to you as if one could not take sulphurous baths excepting in Paris, forgetting in this that he is writing to a physician. Certainly it would not be more difficult at Carhaix than in the Rue St. Lazare to put into a bucket 4 ounces of sulphur and one-half ounce of sulphuric acid, and if one wishes to prepare douches for spraying, it is not difficult to have made a tube of white metal and to fit upon one end a spray to convey the water from the first storey to the ground floor. His article 4<sup>o</sup> *there are indeed other early procedures*, etc., signifies this: "If the patient were under my observation I should apply to his *dartres* different mild caustics and repercutives." He has adopted this practice and makes use especially of nitrate of silver, and indeed in his position it is desirable to cure *dartres* promptly even if it were only for a time. This gives him the vogue especially with the ladies, and as he sees only strangers who come to Paris to be treated, he never sees that which follows. One must acknowledge, however, that the use of these caustics rarely have grave inconveniences. But certainly you are not such a child as to desire that your skin be clean at whatever price as do the greater part of the patients of Alibert.

Your ever devoted confrère and friend,

R. T. H. LAENNEC, D. M.

Third letter.

KERLOUANEC PAR DOUARNENEZ, 18 January, 1820.

In its time, my dear Pérusel, I received your letter of last month, to which the wandering life that I am leading here, while they are almost completely rebuilding my hermitage, has hindered me from answering earlier.

I had learned through Tougoët of your marriage, and I congratulate you, all the more sincerely in that I know that you are a man who can appreciate all things at their true value, that which one cannot say of all people who marry. There is one thing, however, to which in my opinion you ascribe far too much importance: namely, the question of medicine of which you speak to me. I cannot blame you for having followed the advice of Alibert, although (between us) you may be sure that he gave it to you as frivolously as almost all that which he gives to the public: But I think that you would do well to stop there for the moment, and especially to be guarded in the use of mineral depura-

<sup>3</sup> Here several words are crossed out so successfully that one is unable to read them.

<sup>4</sup> Erased but deciphered with the lens.

tives—you know as do I that the long use of sulphur sometimes brings about blood spitting, and you know equally well the inconveniences of another sort of the preparations of mercury.

*Optima interdum medicina, medicinam non agere.* For my own account and for that of others (when I find the people intelligent enough) I follow this maxim of Celsus, in all the little ills which are much more difficult to cure than to endure, and I advise you as a friend to do the same.

I am going to lecture you, however, on this subject, as I promised, and I hope that this will be in the course of the spring.

In the mean time accept the assurance of the sincere attachment of your devoted confrère and friend

R. H. T. LAENNEC, D. M.

There is much in these brief lines on which one might comment or moralize. Especially interesting is the reference in the second letter to the non-contagiousness of phthisis. Laennec is very careful in his statements as to the contagiousness of tubercle. In the manuscript notes for his twentieth lecture at the *Collège de France*, which I was able to examine last summer through the great kindness of Dr. Cornillot, I find the following entry: "Tuberc. sont il contag.? Conlag. des scrophules et des tuberc. crus dans bp de pays. mesures administr. Faits pour et bp plus contre. Observ. de tub aux doigt par inocul. ne pas trop s'y fier: mais certes pas facilement contag. en nos climats."

But later there is added with another pen: "Toutes les malad. contag. peuvent l'être plus ou moins. petite vérole, syphilis, peste elle même, moins vers la fin d'épid, mais contag. n'est pas moins certaine."

This might be translated "Are tubercles contagious? The contagiousness of scrophulosis and of tubercles, believed in many countries. Administrative measures. Facts for and many more against. Observation of tuberculosis on the finger by inoculation. Don't rely on it too much: but certainly not easily contagious in our climate. . . . all contagious diseases may be so more or less—small-pox, syphilis, plague itself, less toward the end of epidemics, but contagious none the less certainly."

In the second edition of his book he discusses the question in much the same way. "Tuberculous phthisis," says he,<sup>11</sup> "has long been considered contagious and is now so regarded in the popular mind, and in the opinion of magistrates and of some physicians in certain countries, and especially in the southern parts of Europe. In France at least, it does not seem to be. One sees often among people of moderate circumstances, a large family sleeping in the same room with a phthisical patient, a husband sharing to the last moment the bed of his phthisical wife without contracting the disease. The woolen clothes and mattresses of the phthisical, which in certain countries are burned and which in France, as a rule, one does not even wash, have never seemed to me to convey the disease to anyone. However, prudence and cleanliness would demand more precautions than are usually taken in this respect. Many circumstances, however, prove that a disease which is not habitually contagious may become so under certain circum-

stances." He then goes on to ask whether a direct inoculation may produce the disease at least locally, and describes an instance in which he infected himself at a necropsy with the subsequent development of an anatomical tubercle. Later he says: "If the question of contagion may be regarded as in doubt with relation to tuberculosis, there is no doubt as to hereditary predisposition."

It is interesting and remarkable that, with his clear recognition of the manner of spread of chronic tuberculosis in the lungs, the repeated fresh outbreaks following so often the softening of caseating areas, the idea of direct inoculation should not have imposed itself upon him more forcibly.

The reference in his first letter to the development of facial spasm following the prolonged used of oil of bitter almond is also interesting. Laennec was so careful an observer that any such statement deserves consideration. I have, however, found no support for the assertion in the literature.

The same might be said of his statement with regard to the influence of sulphur in inducing haemoptysis.

The notes of his lectures at the *Collège de France*, half of which are in the possession of the *Ecole de médecine*, half owned by his great nephew in Nantes, are written on small quarto sheets, 12 cm. square. Each page is divided into two columns, the division apparently made by folding rather than by ruled lines. The main substance of the lecture is in the right-hand column; the space on the left is reserved for notes entered in a small, close hand. The lectures are not written in full. They are rather in the nature of carefully prepared memoranda. Laennec wrote a sort of personal short hand. Many words are abbreviated. Much is in Latin, which is also abbreviated. Some of his abbreviations are interesting. In the termination "ation" the "ti" is often omitted, as in old Latin texts, and written "aon," "dans" is written "ds," "beaucoup" is written "bp," "quelquefois" is almost always written "qfois." Capitalization is often omitted, and punctuation is very crude. The latter peculiarities may, indeed, be noted in the letters which have been reproduced above. In the main his notes are not hard to read while he writes in French. His short-hand Latin is not so easy.

Some of his entries are interestingly epigrammatic. In his opening lecture are notes like this: "Science, ce que l'on sait." "Science, that which we know." "théorie, manière de voir. on ne voir [sic] tout et surtout tout à la fois. Donc, indispensable. mais pas oublier qu'échafaudage, s'en servir comme d'un instrum. prêt à le rejeter et changer dès qu'un fait résiste." "Theory, way of looking (at things). We do not see all and especially all at one time. Therefore, indispensable. But not to be forgotten that, scaffolding, one must make use of, as of an instrument ready to throw it aside and change it so soon as a fact holds its own."

The notes of his twentieth lecture, that on tuberculosis, are deeply interesting. The kernel of the description of pulmonary tuberculosis in the second edition of his book is clearly discernible.

As one glances over the notes of his lectures he is impressed with the clearness of view, the remarkable objectivity and the

<sup>11</sup> *Traité de l'auscultation médiate*, 2me édition, Paris, Chaudé, 1826, I, 649 et seq.

sane and accurate ratiocination. The more one considers Laennec's career the more deeply is he impressed by the greatness of the man and the magnitude of his work. And in thought, in methods, in expression he had that clearness and simplicity that marks the truly great. Here are the closing words of his introductory lecture taken down from the notes in his own hand:

"As for me, I shall not quit the path traced by the medical observers who have successively increased the treasure of science from Hippocrates to our day. If I diverge from some of them I do not fear to say that 'tis from a leaning toward simple observation—even though I may be accused of empiricism. Corvisart was my master, and 'tis perhaps to him that I am indebted for a certain distaste for explanations and theories. I shall make every endeavour to present the facts alone and connected by their most striking analogies, and if

sometimes I am obliged in their exposition, to have recourse to some theoretical, hypothetical views, I trust that it may be evident that I am not insisting upon them, and that I may never put forward my individual opinion for *science*—that is to say, *that which we know.*"

Preceding the presentation of the above paper at the meeting of the Laennec Society on March 29th, 1920, in commemoration of the one hundredth anniversary of the publication of Laennec's book on Auscultation, Dr. Henry Barton Jacobs brought before the Society a complete series of the editions of this book with the possible exception of one or two English translations. Dr. Jacobs is preparing a bibliography of these editions with reproductions of title pages, etc., which will be published later.

## PLEURAL SPIROCHÆTOSIS

By V. R. MASON

(From the Medical Clinic, The Johns Hopkins Hospital)

The following case is reported not only as an example of a disease very rare in America but also as the first instance of spontaneous infection of the pleural cavity by Spirochaeta bronchialis (Castellani) which has been recorded. Inasmuch as certain assumptions, which we have been forced to make in order to explain the sequence of events in this case, are not, at the moment, susceptible of definite proof, a brief discussion of the present status of Castellani's bronchitis will be added from which a comparison of the clinical course of that disease with the symptom complex presented by our patient may be made.

MED. NO. 43919.—Gabriel Banks. White, *et al.* 16. Admitted to The Johns Hopkins Hospital, June 18, 1920.

The patient was born in Austria and came to America when one year old. He had always been a healthy boy. So far as he knows he had not been associated with any individuals who spat blood.

*Present Illness.*—In January, 1920, he had an acute febrile illness which was believed to be influenza. He was not very ill at the time but never recovered completely. His chief complaints were cough with a good deal of expectoration and a constant dull pain under the left shoulder-blade. The sputa were often very foul. During the months following the onset of his illness he was not able to work although he was not confined to bed. On May 23, 1920, he expectorated a small amount of bloody material. The next day he visited the dispensary. Examination at that time revealed remarkably little. A radiogram of the chest showed a few small shadows in the lower lobe of each lung. No sputum was obtained. June 5, 1920, the patient had a chill followed by high fever and severe pain in the left side of the chest. He also noticed marked breathlessness. From this time until admission the patient was very ill. He had exhausting attacks of coughing productive of a small amount of foul sputum. Each night he was delirious and had drenching sweats.

*Examination.*—The patient looked very ill. There were marked cyanosis and dyspnoea. He was very drowsy. The temperature is shown in Chart I. There was an occasional unproductive cough. The breath had a peculiar fetid odor. There were typical signs

of fluid and air in the left pleural cavity. A loud friction rub was audible in the right axilla. Examination of a small mucopurulent specimen of sputum disclosed no spirochaetes.

A needle was inserted into the left pleural cavity and about 60 c.c. of pinkish, milky fluid were easily withdrawn. It had a peculiar fetid odor unlike that of any empyema we had observed. It was examined without staining and found to contain large numbers of pus cells, a few well preserved erythrocytes, some cocci and bacilli and many actively motile spirochaetes. Dark field illumination confirmed these observations. The majority of the spirochaetes were two to three times the diameter of an erythrocyte in length, blunt or pointed at the ends, and actively motile. There were many rather thick coarse forms but a few were very gracile. The number of undulations varied, but on the average four to six were present. A stained smear (methylene blue) of the fluid showed large numbers of bacilli and cocci and many poorly stained spirochaetes. No fusiform bacilli could be found.

Cultures of this fluid and of the fluid obtained at operation were sterile on blood-agar plates and in nutrient bouillon.

On June 19, 1920, a tube was inserted between the ribs (by Dr. A. S. Taylor) and about 700 c.c. of pus were removed. The pleural cavity was subsequently irrigated frequently through the tube with Dakin's solution until the fifth day after operation, when this procedure had to be discontinued on account of violent attacks of coughing followed by collapse probably occasioned by forcing the solution through the perforated lung.

Specimens of the drainage from the pleural cavity, on the second and fifth days after operation, contained spirochaetes in fair numbers. No other organisms were seen and the fluid was again sterile on culture.

*Post-Operative Course.*—The patient was critically ill for several days and his temperature remained high. On the fifth day neosalvarsan (Billion) 0.45 gm. was administered intravenously. The following day the patient expectorated considerable amounts of bloody material which, however, contained no spirochaetes. Improvement from this time was rapid. Injections of neosalvarsan were repeated June 27, July 1 and July 23, 1920. The patient gained in strength and his symptoms rapidly ameliorated. At the present date he has completely recovered except for slight discomfort caused by a partial left pneumothorax.

## COMMENT

We have made a careful search of the literature for cases similar to this—that is, for cases of bronchospirochætosis in which intrapleural complications have developed, but have been unable to find a single instance of empyema with the presence of spirochætes in the pus. Lancereaux,<sup>1</sup> however, has recently reported on an instance of hemothorax caused by a penetrating war wound of the chest in which the bloody fluid contained spirochætes in large numbers apparently in the absence of other micro-organisms. Symptoms of an infected hemothorax were present in his patient, but they were promptly ameliorated by arsenical therapy. He believes, therefore, that the spirochætes, probably introduced by the missile, were responsible for the symptoms and clinical course of his patient.

We believe that the illness of several months' duration

varsan lends some support to the assumption that the spirochætes were at least partially responsible for the clinical course of the disease.

## GENERAL REMARKS

Spirochætal infections of the lungs were first described by Castellani<sup>2</sup> in Ceylon in 1904. He examined two natives who had had recurring hemoptyses for many months. There were very few physical signs from the lungs and they were not suggestive of pulmonary tuberculosis. Specimens of sputum were consequently examined unstained in order to exclude fungus or fluke infections. He found, however, in each instance numerous actively motile spirochætes. His observations were soon confirmed by Branch<sup>3</sup> in the West Indies and by Waters<sup>4</sup> in India. Cases of bronchospiro-

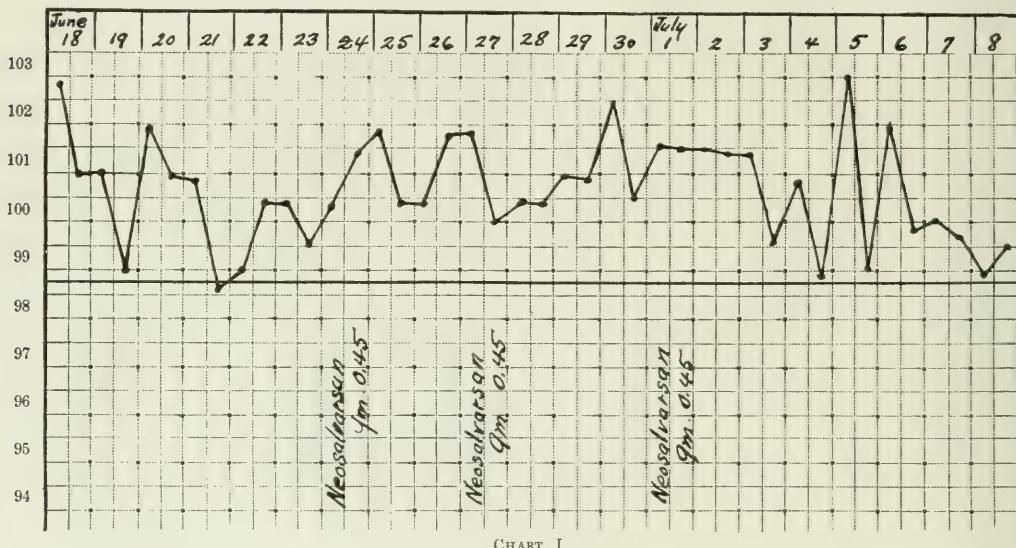


CHART. I.

which preceded the admission of our patient to the hospital was produced by an infection of the lungs with spirochætes. Unfortunately these organisms were not found in the sputum but satisfactory examinations were not made. Nevertheless, the clinical course of the disease and the results of physical examination were very similar to those of bronchospirochætosis. It is probable, therefore, that during an attack of coughing an area of pulmonary gangrene was ruptured and spirochætes were forced into the pleural cavity. Following the formation of a pneumothorax an empyema developed. The pus from the pleural space contained not only *actively motile spirochætae* but many bacilli and cocci. Cultures of the empyema were sterile on several occasions and it is therefore impossible to state what rôle the organisms other than spirochætes played in the production of the pleural infection. The prompt and marked improvement following the administration of sal-

chætosis have been reported with increasing frequency during the last few years. Clinical descriptions of the disease or reports of cases have come from the Philippines,<sup>5, 6</sup> Switzerland,<sup>7, 8</sup> America,<sup>9, 10, 11</sup> Africa,<sup>12, 13, 14, 15</sup> China,<sup>16</sup> Italy,<sup>17, 18</sup> England,<sup>19, 20</sup> Servia,<sup>20</sup> Belgium,<sup>21, 22</sup> Spain,<sup>23</sup> Peru,<sup>24</sup> Holland,<sup>25</sup> Brazil,<sup>27, 28</sup> Cuba<sup>29</sup> and France.<sup>31, 42</sup> It is apparent, therefore, that the disease, formerly encountered mainly in tropical or subtropical climates, has been observed in many countries located in the temperate zone.

The cases reported from France occurred chiefly during the great war and although many of those affected were Europeans, a large number of them had come into contact with Indo-Chinese and native African troops in whom the disease was relatively frequent. Thus in an epidemic of bronchospirochætosis at Toulon (France) Viole observed that, about a month after the admission of Senegalese and Indo-Chinese

affected with the disease, cases began to appear among troops and laborers indigenous to France, who were, however, patients in the same hospital. It is probable, therefore, that the disease is largely transmitted by direct contact with patients and this opinion is confirmed by a number of laboratory infections reported by Fantham.<sup>44</sup>

The organism, *S. bronchialis*, was first described by Castellani<sup>45</sup> and later more carefully by Castellani and Chalmers<sup>46</sup> and Fantham.<sup>44</sup> It varies from  $3\mu$  to  $30\mu$  in length and from  $0.2\mu$  to  $0.6\mu$  in breadth. The ends are blunt or sharp. There are no flagella. The number of undulations varies from 2 to 8; they are never so small, regular or numerous as those of *S. pallida*. The organism is actively motile. It stains well with the usual aniline dyes and especially well with Fontana's stain for spirochaetes. Attempts to cultivate *S. bronchialis* have been uniformly unsuccessful.

The organism is either markedly polymorphous or else more than one type of spirochaete has been observed in the sputum of most of the reported cases. Indeed the case reported by McFie<sup>47</sup> is unique in that all the organisms observed were uniform in appearance. Fantham,<sup>44</sup> however, concluded from a very careful study of *S. bronchialis* and of the mouth spirochaetes that the former, not normally present in the buccal cavity, is a distinct species although markedly polymorphous. He asserts that he has seen coccoid bodies, which he believes represent a resting stage of the organism from which new spirochaetes are formed.

The relation of the spirochaete of Castellani to the spirochaete of Vincent is, at the moment, a matter of considerable doubt. Spirochaetes together with fusiform bacilli have been found in a number of cases,<sup>5, 18</sup> clinically indistinguishable from instances of Castellani's bronchospirochaetosis. In far the greater number of reported cases however no fusiform bacilli have been observed, although they have been sought with some care. It is possible, of course, that both organisms may produce very similar clinical pictures when they succeed in producing lung infections, but that by no means proves the contention of Delamare<sup>48</sup> that the two spirochaetes are identical. The problem, however, must wait for a solution until better methods of differentiating and identifying spirochaetes have been devised.

Attempts to reproduce the disease in animals have met with little success. Chalmers and O'Farrel<sup>49</sup> by intratracheal injections into a monkey of heavily infected sputa succeeded in producing an acute febrile pulmonary infection of short duration and mild course. The sputa of the animal contained many spirochaetes. The results of Delamare,<sup>48</sup> and those of Loygue, Bonnet and Pyre,<sup>50</sup> using other animals, were negative or equivocal.

The recent literature<sup>48-55</sup> contains excellent descriptions of the clinical characteristics of bronchospirochaetosis but it may be advantageous at this time to mention briefly a few important clinical facts.

The acute type begins generally with fever, malaise, headache, pain in the chest and cough. The affection at this stage is indistinguishable by physical signs, symptomatology and X-ray

examination from a common acute bronchitis. Soon, however, the sputa become blood-streaked and not uncommonly frank hemoptyses occur. The breath may have a peculiar foetid odor as emphasized by Nolf,<sup>51</sup> and the disease may simulate very closely pulmonary gangrene. Spirochaetes are usually abundant in the expectorations by the time blood has made its appearance. After a few days, or rarely a few weeks, the cough and fever subside and the symptoms gradually disappear in the milder cases. In others, however, improvement occurs only after the institution of arsenical therapy.

The chronic type of the disease may follow an acute attack or may begin insidiously. The patient as a rule consults a physician on account of recurring bloody expectoration. Occasionally attacks of fever with some asthenia and slight secondary anaemia alternate with periods of comparative freedom from symptoms. The symptomatology, in such instances, resembles closely that observed in pulmonary tuberculosis, lung fluke infections or certain mycotic infections, and a correct diagnosis is reached only after a careful study of the sputa has demonstrated the presence of spirochaetes.

Between the acute and the chronic types many intermediate forms of the disease have been encountered. These may either clear up after several months or may go on into the chronic "pseudo-tuberculous" type (Castellani) of the disease.

Spirochaetal infection of the bronchi in a few instances has been combined with certain other chronic pulmonary diseases. Thus Castellani<sup>52</sup> found spirochaetes in the expectoration of a patient with a mycotic pulmonary infection, and Branch<sup>53</sup> found the same organisms in the sputum of a tuberculous patient. Recently Sinclair<sup>54</sup> in the Hawaiian Islands found spirochaetes usually associated with fuso-bacilli in the sputa of many tuberculous patients who had had hemoptyses. His results, while of interest, have not been confirmed nor correlated with previous observations as yet.

*Treatment.*—The experience of most observers has proved that salvarsan or neosalvarsan in moderate doses promptly and effectively relieves symptoms and brings about a complete cure. Iodides in large doses have also been of distinct value. In many acute cases, moreover, spontaneous recovery has been noted.

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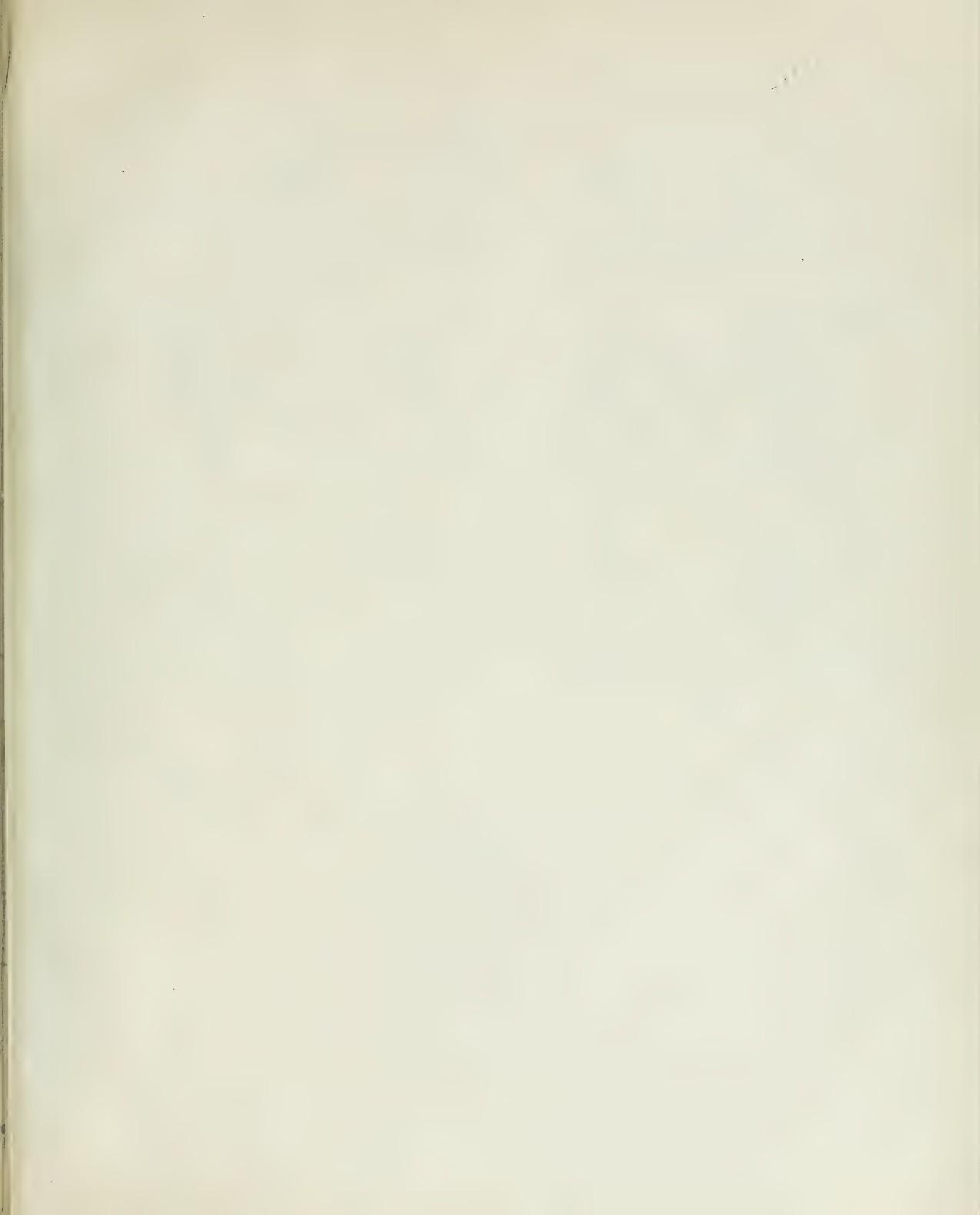
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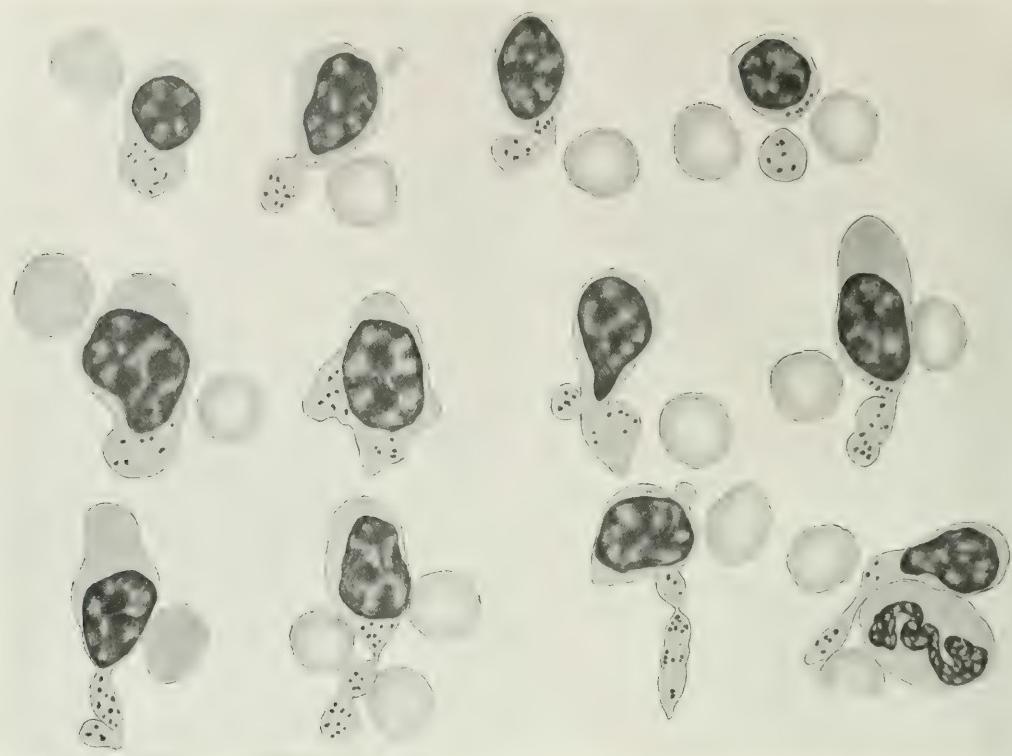


FIG. 1.

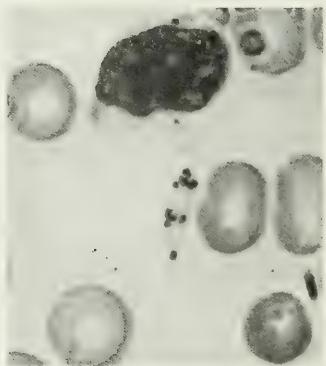


FIG. 2.

## VICARIOUS BLOOD-PLATELET FORMATION

By C. H. BUNTING

(*From the Pathological Laboratory of the University of Wisconsin*)

It is not my intent in this paper to enter at length into a discussion of blood-platelet formation, but to place on record an observation of unusual compensatory or vicarious formation of bodies, analogous, at least, to the normal blood-platelets. Wright's discovery that the normal platelets are formed by the segmentation of pseudopodia projected from the megalokaryocytes of the bone-marrow, seems, in this country, to have had almost unquestioned acceptance as a fact, demonstrated. That in some quarters it is regarded as an unproved theory is shown by the recent writings of certain Italian authors, particularly of Pianese, who does not accept the theory, and of Perroncito, who finds from his investigations no evidence for or against the theory.

I do not wish to reopen the general question further than to say that all the evidence I have been able to obtain from clinical, pathological, and experimental observations, published and unpublished, confirms the findings of Wright for the origin of the normal platelets. The comparative frequency of incompletely segmented pseudopodia and of undivided protoplasmic masses of platelet character in the blood, especially in such conditions as Hodgkin's disease, as emphasized by the author, and in chronic myelocytic (spleno-myelogenous) leukæmia, indicates at once the mode of formation of platelets, and also that the source of the pseudopodia is a cell of greater protoplasmic content than any cell ordinarily found in the blood stream.

That other cells may contribute bodies having the value of platelets, when a platelet-need is established, has been demonstrated by W. H. Brown. He has shown that in the rabbit, after destruction of the megalokaryocytes, certain large multinuclear endothelial cells of the bone-marrow and also the so-called "transitional" cells of the circulating blood may project pseudopodia which segment into platelets. From these experiments he concludes that normally, also, the last-named cells may contribute platelets to the circulating blood, but that the majority of the circulating platelets are derived from the megalokaryocytes.

I have expressed the opinion that the blood-platelets normally do not form a heterogeneous collection of cell fragments but represent a single type of structure as shown by their characteristic staining with Wright's stain. In the examination of literally hundreds of blood-smears from man and animals, I have found no evidence contrary to this opinion and until recently no evidence of any other origin of platelets, if one may except the suggestion offered by a very occasional pseudopodial projection from a transitional cell. These have been so infrequent and usually so small that there has always been doubt as to whether they were genuine or artefacts created in making the spread. However, in a study of the blood of influenza patients of the 1920 epidemic, I have encountered

what appears to me indubitable evidence of the compensatory formation of platelets or platelet-like bodies from leukocytes of the circulating blood. I speak of this as a "compensatory formation" for the reason that in influenza there is apparently a sharp inhibition of bone-marrow activity with a marked fall in the number of circulating platelets as one of the results. In blood-smears from early cases, platelets are very few. Agglutinated masses are almost lacking in the smears, and only scattered, isolated platelets are seen. These observations are borne out by the published counts of platelets in influenza by Kinsella and Broun.

The blood of one such case, with the characteristic leukopenia and with extreme reduction in number of platelets, offered a picture, unique in the author's experience. Practically every large lymphocyte in the smear showed some stage in the formation of pseudopodia or platelets. It is realized that in using the term, "large lymphocyte," confusion will be created unless the term is defined. By the term is meant not a member of the large mononuclear-transitional group, nor the pathological large lymphocyte (lymphoblast), nor the intermediate-sized lymphocyte occurring in lymph-gland stimulation, but a cell, common in normal blood-smears, which is apparently a mature form of the small lymphocyte. At least, it is a cell with a nucleus the size of that of a small lymphocyte, but with more protoplasm, which has an acidophilic staining-tendency and contains a few coarse, often rod-shaped, azurophilic granules.

In the smear in question, some of these cells showed merely the collection of the granules about a point in the periphery of the cell; others, a slight protrusion of this part of the protoplasm; others showed the cutting-off of the granule-containing mass, while still others showed the formation of definite pseudopodia of considerable length with grouping of the granules as in platelets and with beginning constriction of the process evident. A reference to the camera lucida drawings in Fig. 1 and to the photograph of a single cell in Fig. 2, may possibly give a better idea of the nature of these changes than can be obtained from a verbal description.

It was also noted in the smears that these lymphocytes had apparently acquired an increased adhesiveness over that normally seen, and in this case, a condition not shown by the other forms of leukocytes. Careful study of the preparations, however, eliminated from the author's mind the possibility that this adhesiveness was responsible for the production of the pseudopodia as artefacts. The clumping of the granules, the beginning constriction of the pseudopodia, the varied direction of extension of the processes, the absence of signs of stress in cells close by, all indicated that here one was dealing with the production of platelet-like bodies, differing slightly morpho-

logically but probably possessing the same functional value as indicated by this very adhesiveness.

A similar process was noted in the blood of several other influenza cases, but in no case was there an approach to the extensiveness of the process, noted in the case described.

The drawings in Fig. 1 were made by the author and his thanks are due Dr. V. C. Jacobson for the photograph in Fig. 2.

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## THE MEASUREMENTS OF INTRACRANIAL PRESSURE CHANGES IN AN EPILEPTIC AND ITS EXPERIMENTAL VARIATIONS

By FRANKLIN G. EBAUGH and GEO. S. STEVENSON

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This study was planned after a series of observations of the changes in intracranial pressure in an epileptic had been made, at the suggestion of Dr. Meyer. These changes in intracranial pressure were first observed through an area of bone defect without the use of any recording device, a rise of pressure being noted to precede convulsive seizures, and the duration of increased pressure after attacks being timed and recorded.

This area of bone defect in our patient suggested an opportunity not only for measuring variations in intracranial pressure, but also for measuring changes due to the administration of solutions of various concentrations. Furthermore, working on a human subject provided an opportunity for connecting the experimental data concerning changes in brain volume in animals<sup>1, 2</sup> with changes in intracranial tension in man. Since no anesthetics were necessary this factor is eliminated from our results.

Weed and McKibben found in experimenting on anesthetized animals that the intravenous administration of solutions of various concentrations gave an increase or decrease in brain volume according as they were hypotonic or hypertonic, respectively.

Our patient, B. H., is 33 years old, an electrical engineer of considerable ability. The onset of his present illness dates from 1913, when he complained that he frequently had difficulty in talking and transitory periods of haziness of consciousness. These attacks were all preceded by a perception of a definite, peculiar odor, which he described as sweetish but not unpleasant. He grew much worse gradually, and in the early part of 1914, while at work, he had his first spell of unconsciousness. This attack was instantaneous, and although he thinks he noticed a peculiar smell preceding it, he is not sure. He had an amnesia for this attack, and fell on his face with injury. Soon after this attack he accepted a position in an important engineering project. During the next three months, he felt much better; he had frequent petit mal seizures, but no convulsions. He worked very hard and was confined much of the day. In May, 1914, his unconscious spells and convulsions became more frequent and he was forced to give up his position. He usually had an olfactory aura before each attack, which began with a cry, and lasted from 5 to 20

minutes, and usually included tonic and clonic convulsions. These convulsions were not accompanied by salivation and biting of his tongue. There is no history of incontinence. He suffered from amnesia before the attacks and at times had difficulty in finding the correct words while talking. He returned to the United States, and in June, 1914, a left exploratory craniotomy was performed by Dr. Dandy, of The Johns Hopkins Hospital. The left Rolandic area was exposed and a subarachnoid cyst was evacuated. A definite thickening of the pia arachnoid was present. He showed little improvement following the operation. During 1915 and 1916, he occasionally had convulsions. He continued to have difficulty in finding the correct words in talking. He took up Christian Science and at times felt much encouraged, and returned to work for short intervals. He frequently injured himself during attacks, occasionally he bit his tongue; no frothing nor incontinence was observed.

He was admitted again to the surgical service, April, 1917. At this time his difficulty in speech was thought to suggest a motor type of aphasia, and he gave as his complaint difficulty in talking, thinking and hearing. Convulsions had usually occurred at the rate of from one to two per month. They were not followed by headache; he usually felt relieved afterwards and was able to return to work. In May, 1917, Dr. Heuer performed a left craniotomy and evacuated a subarachnoid cyst. One week later he had a generalized convolution in which he struck his head. No aura preceded this attack and it was followed by general weakness and numbness of the right side. He was discharged with no further treatment.

There was no change in the character of the convulsions after the second operation. The patient attempted clerical and mathematical work but found himself handicapped by difficulty in thinking and by periods of forgetfulness and stupidity. A sub-temporal decompression with opening of the dura in June, 1918, brought no improvement. The attacks had increased in number to an average of from one to three per week at the time of admission to the Henry Phipps Psychiatric Clinic, November 20, 1919. During the first month in the hospital the patient had 10 generalized convulsions. He could tell of no definite aura, but on several occasions he said that

he had a funny feeling in his head. He gave the characteristic initial cry followed by general tonic and clonic convulsions, with his mouth open and staring straight ahead. He did not bite his tongue but occasionally received severe injuries through falling. He rarely frothed at the mouth and incontinence rarely occurred. His pupils were fixed to light and frequently he showed a bilateral positive plantar response. The attacks usually were of 5 to 20 minutes' duration and were not followed by periods of sleep. The patient was observed to be less tense and depressed after the attacks. He had frequent petit mal attacks, characterized by momentary loss of consciousness with pallor. There was a definite amnesia with all the attacks. During his stay in the hospital, the patient continued having from 1 to 7 convulsions per month. He averaged from 5 to 10 petit mal attacks each month. He showed an interesting speech difficulty which he explained as follows: "I know what I want to say but I can't think of the right word." On frequent occasions he complained of inability to derive any meaning from what he read. His spelling of test words was definitely faulty; the repetition of given words was slow and inaccurate. He showed a slight retention difficulty in giving the gist of short stories which he had read previously. He showed periods of restlessness during which he complained of feeling depressed. He was unable to describe the events of his illness in sequence, and his statements differed from those given by relatives. The memory defect was usually in proportion to his difficulty in expressing himself correctly. In the main he showed fair retention, grasp of general information and calculation, judgment and insight. The patient was very suggestible and he was enthusiastic over any new attempt to treat him. In our experimental work it was necessary to take into account this suggestibility, so he was not informed of the results we expected, or given any of the facts as to the nature of subsequent work. Any change in treatment resulted in subjective improvement. He was not given bromide treatment, and the attacks did not occur as frequently as at home. Starvation periods seemed to help him somewhat. His general physical status was good.

The neurological examination showed loss of smell in the left nostril. In both eyes the veins were full and tortuous; the margins of the discs were distinct.

Blood examination: R. B. C. 4,800,000. W. B. C. 8000. Hb. 90 per cent. Normal differential count.

Spinal fluid examination: Negative.

Gastro-intestinal series of X-ray pictures proved negative.

Our patient readily cooperated with all experimental work, even after it was explained to him that it would cause much inconvenience on his part.

#### APPARATUS AND METHOD OF APPLICATION

The registering device consisted of an inverted tambour covering the area of bone defect, and connected with a manometer or a kymographic outfit.

The tambour was the usual type, being a short cylinder (Fig. 1) 5 cm. in diameter and varying in length with the contour of the open end from 1 to 1.5 cm. In order to secure

a good application of the tambour to the margin of bone around the defect, a plaster negative of this region of his head was made in the Orthopedic Department. From this a clay positive was made and used as a model. The edge of the tambour over which the rubber was drawn was made to fit the contour of this model. At a point 6.5 mm. from the closed end of the tambour a flange was soldered on, in order to secure the dam, and between this and the closed end a rubber band was cemented around the tambour, so that the cords binding the dam might have a soft surface in which to burrow, and make the junction air-tight. From the flat surface of the tambour—the closed end—there were two outlet "L" tubes directed oppositely, and at about 45° to these brass wire eyes projected from the tambour, for the attachment of the strap with which the instrument was held to the patient's head. This strap consisted of 3 cm. wide web, such as is used in head extensions, sewed to the eyes on the tambour and buckling over the opposite (right) temple. The rubber dam used for the head tambour and for the recording tambour was of light weight. A piece of this was also put between the head tambour and the patient's scalp, in order to prevent the rotting of the tambour dam.

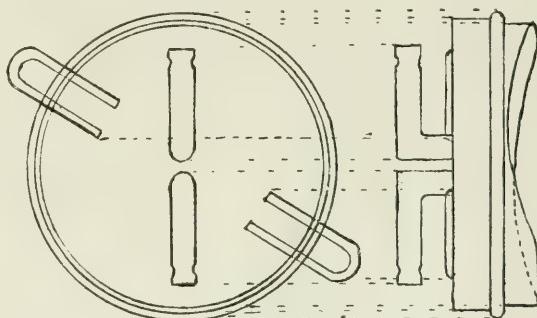


FIG. 1.—Diagram of tambour applied to the patient's head.

The manometer was a U-tube of 2.5 mm. caliber enclosed in a wooden case so as to be portable, and registering up to 150 mm. water of pressure. One end of this U-tube was connected to an outlet tube of the head tambour. In order to prevent kinking the outlet tube pointing downward was used. On the other end of the U-tube was a short piece of rubber with a screw clamp on it, to prevent fluctuations of the manometer when not being read, since certain activities of the patient, as coughing, would cause the manometer to overflow. Water was used as the displaced column in the manometer. Connections were made with red rubber tubing and tightened with a ring of copper wire.

From the other outlet tube of the head tambour was a free rubber tube of sufficient length to allow the patient to move in bed. When the manometer was in use, this was clamped off close to the head tambour. When the kymographic recorder was used, the manometer was clamped off and this free tube was attached to the recording tambour on which the lever rested which marked on the kymographic drum.

Owing to the fact that the kymographic attachment considerably increased the air space of the system, at the usual pressure was not very sensitive, and offered another opportunity for leakage of air, this was clamped off when manometer readings were being taken; and since manometer readings at the pressure required for kymographic record were very low, the manometer was clamped off when tracings were obtained.

As a result, perhaps, of the permeability of the rubber, there was a fall of pressure in the system during 12 hours of usually about 10 mm. when set up off the patient's head, at the pressure existing when applied, *i. e.*, 70 to 80 mm. Immersion in water did not disclose any other cause for this escape of air.

In order to calibrate the tension of the rubber dam for comparison when changes were made, the manometer head tambour system was closed at atmospheric pressure, and the effects of various weights, ranging from 5 to 5000 gm., put upon the dam were recorded. Subsequently it was found that practically no difference in tension existed after change of the dam. As no stretching was needed this was expected.

The bone defect of the patient is situated just above the left temple, giving an excellent opportunity for a firm fixation of the tambour. Since the dura had been opened the area of bone defect presented a fair degree of elasticity, enabling us to follow pressure changes at a close range. The method giving the most constant results was to lay the protective rubber over the defect, apply the tambour so that its contour fitted the head, have the patient report on the comfort of the contact and, if satisfactory, hold it in place. The posterior strap was then passed under the occipital protuberance, above the right ear, meeting the anterior strap at the temple over which it was buckled. The anterior strap passed over the forehead just below the hair line. In buckling it was important to hold the straps in position to prevent slipping, and to judge the tightness by the force used and the wrinkling of skin beneath the buckle (Fig. 2). The feelings of the patient were found to be a good indication of a proper application, and after getting used to it he assisted considerably in this. Although he had some discomfort from the head gear at first, he was soon able to sleep with it on. With a good contact the instrument stayed in place well. When pressure readings were desired, before application the head tambour was disconnected from the kymograph system, the free tube was opened to permit the manometer to register zero and then clamped off. The instrument was applied with the patient in a sitting position, his head turned with the defect pointing up, readings being taken from the manometer with the patient sitting erect and also while he was lying in the lumbar puncture position. These readings represent of themselves no absolute values but are arbitrary along with the original zero pressure. Since the manometer readings vary considerably with change of posture these two postures were adopted.

In order to determine the error of application of the head tambour, ten successive applications were made. These gave 60, 55, 55, 65, 62.5, 52.5, 62.5, 55, 60, 55, averaging 58.3, with a maximum deviation of less than 7.5 mm. and a maximum variation of 12.5 mm. On other trials even better results were

obtained. In applying it for experimental work three trials were made, and, if satisfactorily close, a subsequent application registering the average of the three was used. Faulty applications showed an ascent of pressure readings until a self-adjustment took place. A proper application showed no such change.

Comparison of the arbitrary readings with actual pressure was made by applying the apparatus, putting the patient in the lumbar puncture position, taking readings over a short period, and then performing a lumbar puncture and taking readings from a gauge attached to the needle at the same time as from the manometer. The spinal fluid was gradually run off to zero and then returned.

The results of simultaneous readings of spinal fluid pressure and pressure registered through the head tambour are as follows:

	Head manometer	Spinal fluid manometer
Applied to head.....	85 mm.	
Punctured (escape of about 2 c. c. of fluid) .....	80	
Cock opened .....	70	110
	70	95
	65	95
	65	90
	67.5	70
	62.5	60
	60	45
	55	45
	55	0
Fluid returned .....	52.5	105
	60	

The original reading of 85 dropped to 80 as some fluid was lost in connecting the gauge, and to 70 as the gauge filled up. At zero spinal fluid pressure it was 55 but fell to 52.5 as the fluid was returned. This probably represents the actual zero point for the point in lumbar puncture position and was caused by delay in the displacement of the fluid. The return to 105 in spite of the 4 c. c. being retained for examination suggests either a delay in redistribution or else a rather rapid resecre-  
tion of fluid. These readings are of great significance, since it is obvious that the changes in pressure in the recording system applied to the area of bone defect in the head represent only relatively the changes in absolute pressure in the cerebro-spinal fluid. Such changes as were recorded by the head manometer may, however, be considered as indicative of corresponding changes in the cerebro-spinal pressure. A fall of 10 mm. in the head tambour is equivalent to one of 30 mm. in the cerebro-spinal pressure.

#### INTRACRANIAL PRESSURE CHANGES AND KYMOGRAPHIC TRACINGS

Investigations were directed towards:

- (1) A study of gross changes in intracranial tension. (2) A study of manometer readings. (3) A study of kymographic tracings.

During April and May, gross observations on changes in the depth of the area of bone defect revealed filling or increased

pressure preceding, during and following nine out of ten convulsions. It is probable that our percentage would be 100, if the other attack recorded had been examined for pressure changes. On other occasions a definite relation was noted between this increase in pressure and the patient's general condition, since he frequently complained of feeling as if an attack were coming on when the filling was marked in the area of bone defect. Often he appeared tense and depressed during these intervals with a general improvement in his mood following a return to normal pressure. Pressure changes were also noted before petit mal seizures. These were less pronounced than during grand mal attacks. This was especially noticeable on April 19, when the patient had three petit mal attacks. On this day transient increases in pressure were recorded on five different occasions.

It is interesting to note that this increase in intracranial pressure is associated with increase in blood pressure.<sup>8</sup> Twice we were fortunate enough to obtain readings just before the onset of a generalized convolution. These readings averaged 20 to 30 mm. of mercury higher than control readings. On several occasions the tension appeared marked, with bulging in the middle of the bone defect simulating herniation. The patient complained of tinnitus and headache. Although the eyegrounds were examined, no edema or evidences of increased intracranial pressure were observed when he made these complaints. On rare occasions he complained of a peculiar odor and taste, but on examination he named the test solutions correctly.

The accompanying chart shows the time relations of increased tension. Only readings observed before experimental variations in intracranial tension were obtained are given.

Date	Attack	Duration of increased pressure
March 28..	Grand mal..	.6 minutes.
March 29..	Grand mal..	.7 minutes.
April 1..	Grand mal..	4½ minutes.
April 14..	Grand mal..	Increased—but not timed.
April 19..	3 petit mal..	Intervals of 12 minutes.
		Intervals of 22 minutes.
		Intervals of 5 minutes.
April 21..	Petit mal....	One hour before attack.
May 3..	Grand mal..	.45 minutes.
May 7..	No attack	
		observed.
		Complain-
		ed of feel-
		ing badly.
May 10..	Grand mal..	Intermittently for next 3 days.
May 13..	Petit mal....	Increased—but not timed.
May 21..	Depressed ..	Increased—but not timed.
May 23..	Grand mal..	3 minutes, and intermittently for next two days.

When the manometer was used, the instrument was applied in the usual way. The patient was allowed to go about the ward in his usual activities, sitting down for readings every 15 minutes. Being an engineer, he was able to do most of the recording himself. Occasional readings were taken with the patient in the lumbar puncture position. The readings were continued usually over a period of eight hours and were recorded on cross-section paper. From these data several

things could be noted; first, the relation of the two positions; secondly, the daily and hourly variations in the individual curves, and third, a study of a composite curve, averaged from all those obtained.

The sitting posture was found to bear a definite relation to the lumbar puncture posture. Most of the readings, when the patient was seated, fell within 45 to 85 mm. of water. The pressures in the lumbar puncture posture were grouped for each 5 mm. pressure, in the sitting posture, within the 45-85 limits, and these pressures were averaged for each group. It was thus found that the differences in the two postures at different pressures were practically the same, ranging from 35 to 40 mm. and averaging 37.5. Beyond these limits our readings were fewer, and no constant relation could be made out.

A study of the curves themselves shows very little. There is a suggestion that activity tended to raise the pressure. On one occasion there was a gradual fall in pressure of 10 below the average, while the patient was eating a meal, with a gradual rise afterwards to 10 above. On another occasion after a 5½ hour variation of only 5, on his going to the dental clinic for a filling it rose 10 mm. above his previous maximum and then fell 25 mm. There was a constant tendency towards a fall at the end of the day. We have here a set of facts which we feel are worth recording, but which we have not attempted to control or interpret. The finding of a rhythmic fluctuation in spinal fluid pressure, through kymographic tracings to be discussed further on, would lead us to expect periods of fluctuation and periods of stability in manometer readings.

A study of the normal composite curve, made from an average of all the normal curves, shows very little outside of its evenness, and a slight fall toward the end of the period of observation. No importance can be placed upon the latter feature, since, as we have previously noted, the rubber is slightly permeable, and liable to show the same fall when under the same pressure off the patient's head.

Although our manometer readings, relative to epilepsy itself, are too isolated to warrant generalizations, it is interesting to note that, on one occasion when the patient was dazed and speech was difficult, the intracranial pressure was increased over a period of 4½ hours, during which he had three petit mal attacks. On another occasion he had seven grand mal attacks in 48 hours, followed by a period of four days during which he was in bed, dazed. During this whole period the bone defect showed bulging. The manometer on these days read 120, 120, 120, 125, respectively, with much increased pulse excursions. On the fifth day it read 110, and fell very gradually to 70 as the patient got up and went about. After 13 hours in bed it had again risen to 105 and fell gradually after he got up again. These manometer readings represent far greater intracranial pressure changes, as has been explained previously. The slow return of pressure to normal limits after lying may in this state be of significance, since ordinarily it required practically no time to adjust itself.

By resorting to kymographic recording, we were able to detect, from second to second, changes which could not be made

out otherwise. There were thus revealed three types of waves (Figs. 3 and 4): First, a normal arterial pressure tracing; second, a normal respiratory variation, and, third, a wave definitely but irregularly rhythmic, averaging about 90 seconds each, but varying greatly in time. These last waves were of two types. First: There were groups of nicely rounded shallow waves, a little more frequent than the average and occurring in pure culture (Fig. 5). The second type showed a slow rise, suddenly forming a peak and then a sudden fall (Fig. 6). These likewise occurred in groups. It is of interest to compare both these types with some of Carlson's records of gastric contractions,<sup>4</sup> where identical waves are found. These waves not only occurred in groups but there were intervening quiescent periods (Fig. 4). They were first noted at night while he was asleep, six hours after his last meal. They were noticed most clearly after a period of starvation especially those of the second type. Synchronous gastric and intracranial pressure tracings (Fig. 7) show a relation between changes in the two (Fig. 7). This is probably on a vasomotor basis, as suggested by Carlson. Evidence points to an association here.

There were certain definite activity curves of a constant form. Clearing of the throat or coughing always produced a sudden rise and fall, followed by a slight rise and gradual fall. A prolonged increase of intrathoracic pressure produced a high plateau.

The act of urination showed an initial and terminal rise usually with rises in the midst of the act. The straining accounts for the rises. Deep breathing merely accentuated the respiratory waves. Snoring did this even more. Holding the breath after a deep inspiration shows a very typical curve (Fig. 8), for example, a rise consuming 5 seconds followed shortly by a fall consuming 4 seconds, then a rise during 6 seconds to a higher level and a slight fall during 4 seconds. After running level for 30 seconds longer a rise and gradual transition into extreme fluctuations associated with respiratory movements of the chest occurred and lasted till the end of 90 seconds, when the patient took a breath; a prompt fall followed, a sudden rise again and a gradual fall during the next 15 seconds. When respiration was stopped at different phases, a typical curve resulted. When stopped at the end of expiration it was less shallow, and more irregular than at the end of inspiration. Even the act of swallowing produced a typical curve—a sharp peak upward with a shorter one downward.

On two occasions we were able to record petit mal attacks. These records were similar in their form, the typical feature being a rapid rise associated with an increase in amplitude, which we were unable to duplicate experimentally. One of these (Fig. 9) occurred after a 7-minute period of study, and persisted for 3½ minutes. The rise with increased amplitude and fall to normal level lasted over one minute. During this time the patient lay still and stared ahead. During the next 2½ minutes he gave responses which he could not remember later. He then became fully conscious, but for 3 minutes there were irregularity and increased amplitude. On a third record taken when the patient felt as if he had aborted an

attack there was a sharp rise and fall, covering 5 seconds, followed by an increased amplitude and irregularity. There was no apparent loss of consciousness.

Robbins<sup>5</sup> has recently demonstrated similar changes in intracranial pressure during various activities, such as sniffing, stammering, etc., which he found were always associated with an increase in brain volume. He found also that shock, fear of stammering and emotions of every kind caused an increase in brain volume, accompanied by increased size of pul. Angelo Mosso<sup>6</sup> has also shown the effects of the emotions in producing cerebral vascular changes. He investigated the movements of the blood vessels and bladder movements with the plethysmograph and found waves coinciding with the respiratory movements. When he investigated blood pressure changes he obtained fluctuations as described by Traube. The respiratory curves exhibited periods of greater or less activity depending on the activities of the patient. Leonard Hill<sup>7</sup> obtained similar curves and demonstrated the dependence of intracranial pressure on the general arterial and venous pressure.

#### CHANGES IN PRESSURE PRODUCED BY SOLUTIONS OF VARIOUS CONCENTRATIONS

The object of this study was to determine if we could establish a link between the experimental data concerning change in brain volume in animals and man. We desired to confirm Weed and McKibben's<sup>1, 2</sup> work, which dealt with changes in brain volume in cats. We were fortunate in having a trephine opening present and that no anaesthesia was used. We were fortunate, also, in that our patient co-operated from the very beginning of our work, and we were able to obtain data of subjective changes along with objective manifestations. We could take readings over long periods of time, and follow variations in intracranial pressure under more ideal conditions than would be possible with animals. During all our work, however, nothing of an experimental nature which would result in any marked change in the patient's general condition was done. For this reason we did not attempt to control our manometer readings, obtained over the area of bone defect, by repeated lumbar punctures, although this would have enabled us to follow the pressure changes in the cerebrospinal fluid at a closer range. We have relied entirely on our previous standardization of the relation of intraspinal pressure to our manometer readings; thus we have obtained only relative cerebro-spinal fluid pressure readings. Pressure readings taken over the area of bone defect, owing to the resistance of the skin and dura, represent far greater changes in intracranial pressure than can be recorded by our tambour.

The changes produced in intracranial pressure were observed by simple observation of the bulging as well as through manometer readings obtained by the method previously described. It is interesting that these changes were frequently commented upon by the patient himself, who used them as a gauge for his activities. When he felt badly he learned to feel his head, and if he noted filling in the area of bone defect he usually remained in bed or in a protected position. On

these occasions he frequently gave typical complaints, as follows: He felt as if an attack were coming on; at times he noticed a peculiar odor; his head felt full; he complained of tinnitus; feeling shaky all over, etc. When the area of bone defect was depressed, he was usually brighter, more alert, spending his time working at various mathematical problems and reading an elementary astronomy book. These findings suggested that future therapeutic applications could be made, especially if we could obtain constant changes in intracranial pressure by giving hypertonic and hypotonic solutions.

In choosing our solutions, we followed the lead of Weed in using a hypertonic Ringer's of the following formula:

Sodium chloride .....	18 gms.
Potassium chloride .....	.085 gm.
Calcium chloride .....	.50 gm.
Water .....	100 c.c.

We also used a 30 per cent glucose solution. We used tap-water for our hypotonic solution. After first determining our patient's capacity, we were surprised at the beginning that he could take from 4000-5000 c.c. of water in the course of 1½ hours, and chose 4000 as our unit. The patient would drink 1000 c.c. at the beginning, 200 c.c. every five minutes up to 4000 c.c., making an interval of 1½ hours. We used normal salt as our isotonic solution, giving this as a control in the same amounts as for hypertonic and hypotonic solutions. All of these solutions were given by mouth with the exception of the hypertonic glucose, which was administered intravenously. In the case of hypertonic solutions, they were all administered in quantities of 200 c.c.

We followed the same method for obtaining our readings as for actual measurements of changes in pressure commented upon previously. Our patient was allowed to go about the ward, as usual, and no solutions were given until after manometer readings had been taken for an hour or more, demonstrating that no leaking had occurred and that the application of the tambour to his head was satisfactory.

*Hypertonic Solutions.*—We found that following the oral administration of hypertonic Ringer's (19 per cent) a constant fall of intracranial pressure resulted. This fall usually began within 15 minutes and continued for an average of 1½ hours. There was a fall from 15 to 20 mm. of water and this was followed in all experiments by a subsequent rise of pressure over a period averaging 3½ hours, when the initial pressure was reached. Later this rise of pressure exceeded the initial pressure. These changes were found to be a constant occurrence, as is demonstrated in Fig. 10 by the composite curves of seven experiments and also of a typical curve. This fall of pressure represented a far greater decrease in intracranial pressure owing to the resistance and inelasticity of the skin over the area of bone defect.

After the administration of the solution, the patient complained of intense burning in his throat and epigastrium usually of 2-4 hours duration. A constant catharsis resulted. Pallor was always present and the patient complained frequently of weakness. On several occasions he gave his characteristic complaint of feeling shaky, of being confused at

times, of finding it hard to express himself. He did not complain when the terminal rise of pressure occurred. For the practical therapeutic application of this method for the transient reduction of pressure, however, this terminal rise of pressure must be taken into consideration, as well as the unpleasant subjective symptoms.

We were unable to try out other hypertonic salts on an extensive scale. On one occasion when high pressure was noted in the area of bone defect, we obtained striking results after the administration of one and a half ounces of sodium

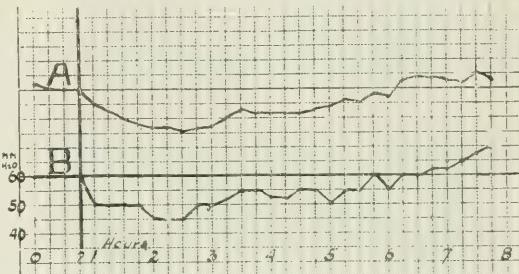


FIG. 10.—A, composite, and B, typical curve of intracranial pressure changes produced by the oral administration of 200 c.c. of 19 per cent Ringer's solution.

sulphate given in 200 c.c. water. An instantaneous fall of pressure resulted, reaching a maximum of 50 mm. pressure in the next hour (Fig. 13). This fall most likely means a fall to zero pressure in the cerebro-spinal system. There was no subsequent rise in pressure during the course of 9 hours. Of course these changes were accompanied by a marked catharsis, and the dehydration resulting may be an important factor in lowering intracranial pressure.

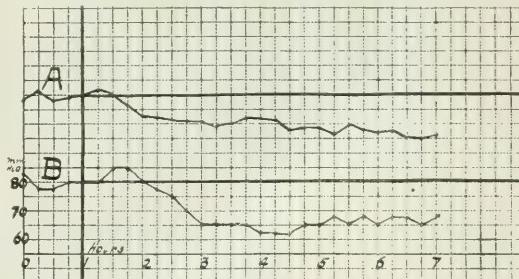


FIG. 11.—A, composite, and B, typical curve of changes of intracranial pressure, produced by the intravenous injection of 200 c.c. of 30 per cent glucose.

*Hypertonic Glucose.*—In dealing with a solution of glucose, it must be borne in mind that the diffusion time of glucose is three times that of salt and the osmotic pressure is proportionately less.

While the changes resulting from intravenous 30 per cent glucose were not as striking as those from hypertonic Ringer's, the findings were constant and no terminal rise in pressure occurred even after 8½ hours. This fall in pressure averaged

15 mm. as a maximum (Fig. 11). With hypertonic glucose, the fall in pressure was more gradual and prolonged than in the case of hypertonic Ringer's. There was a fairly constant, transient, initial rise in pressure following the administration of hypertonic glucose.

The patient had no unpleasant subjective symptoms following the intravenous injection of this solution. The time of injection varied between 12 and 20 minutes. A slight flushing of the face always accompanied the injection. There was no subsequent diuresis and the patient gave no evidence of somatic changes except on one occasion when he had a chill one hour after the injection. He complained of intense headache, and of pain in his back and legs. His temperature rose from normal to 101.2°. He had a leukocytosis of 14,260. The urinary examination was negative. This reaction subsided completely in the course of three hours and was the only untoward one he exhibited.

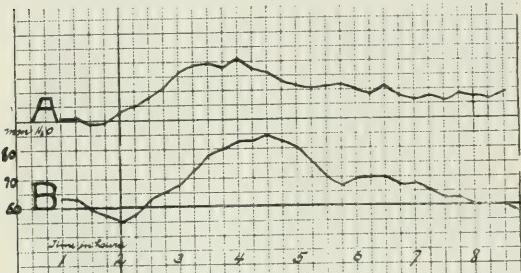


FIG. 12.—A, composite, and B, typical curves of intracranial pressure changes, produced by the oral administration of water (4000 c. c. in 75 min.).

We feel that the results obtained with hypertonic glucose indicate a definite advantage of the clinical use of this solution over hypertonic Ringer's. A more prolonged fall of pressure resulted without subsequent increase, and the patient had fewer unpleasant symptoms. The use of this substance is rapidly becoming more general and the results are often striking as Haden<sup>8</sup> has shown in his article.

**Hypotonic Solution.**—We obtained an average rise of 20 mm. (water) following the oral administration of 4000 c. c. of tap-water. During the ingestion of the water a gradual rise in pressure resulted and continued for an average of three-quarters of an hour after the last 200 c. c. were taken. This is shown in a composite curve of five experiments along with a typical curve (Fig. 12). This rise in pressure was always followed by a gradual fall to the initial pressure during the course of two hours. On one occasion by forcing water to the limit, 8000 c. c., over a period of six hours, we were able to obtain a uniform maximum of pressure with no fall.

The patient seldom complained while taking the water, although afterwards he complained of fullness and frequent urination. This diuresis was noted to be synchronous with the fall in pressure to the initial reading. When the pressure was at its maximum he gave typical complaints. On all occasions he complained of a feeling of fullness in his head

and of intense tinnitus. Frequently he complained of headaches and of feeling as if an attack were coming on. On one occasion an actual grand mal attack resulted after a fairly stationary increase of 20-30 mm. pressure. It is interesting to note that this attack occurred during sleep, and that preceding the drowsiness the patient complained of a terrible headache.

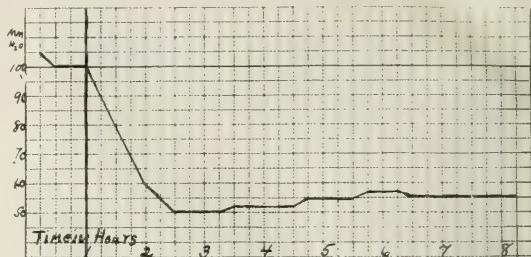


FIG. 13.—Curve obtained after giving hypertonic sodium sulphate showing a drop in pressure of 55 mm. Maintained for an interval of 8 hours.

#### CONTROL READINGS

We attempted to control our results by: (1) A series of readings with the patient in his usual activities; (2) isotonic solutions administered in the same quantities as used for hypertonic and hypotonic solutions.

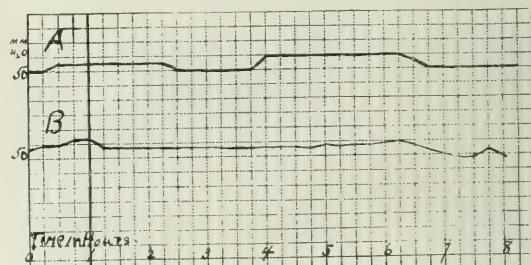


FIG. 14.—A, control curve—4000 c. c. of 85 per cent sodium chloride which controls volume of fluid given orally for both hypertonic and hypotonic solutions. Curve shows a maximum variation of 5 mm. pressure. B, composite of 8 curves taken with subject in usual activities.

For our normal control a composite of eight readings (Fig. 8) shows a maximum variation of 8 mm. However, this fall occurred late in the day and we have found a similar result from probable permeability of the rubber dam.

In order to control our experiments, in which we used hypertonic Ringer's solutions and hypotonic solutions, we used 4000 c. c. of normal saline solution. This was given by mouth. Our control curve (Fig. 14 A) shows a maximum variation of 5 mm. in pressure. Normal saline given orally of the same volume as the hypotonic solution adequately controlled this experiment. Since this is equivalent to 20 times the volume of our hypertonic solutions administered orally it also furnishes a definite control for our experiments with hypertonic solutions.



FIG. 2



FIG. 3



FIG. 4



FIG. 5



FIG. 6

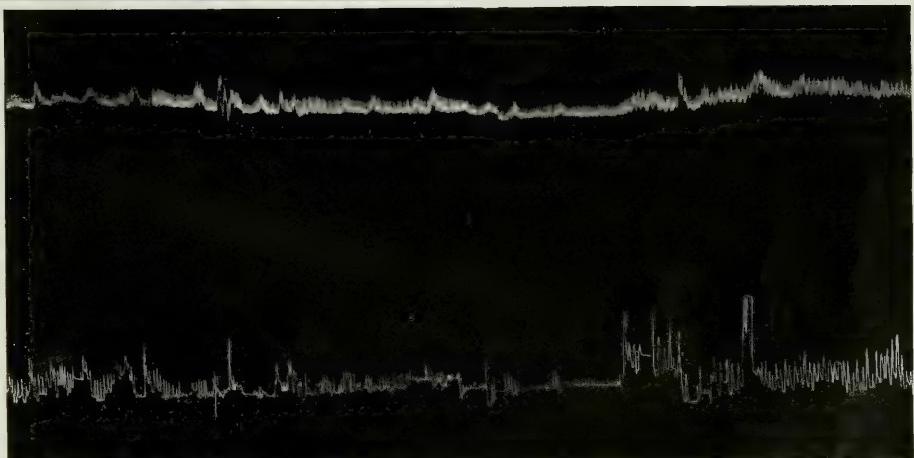


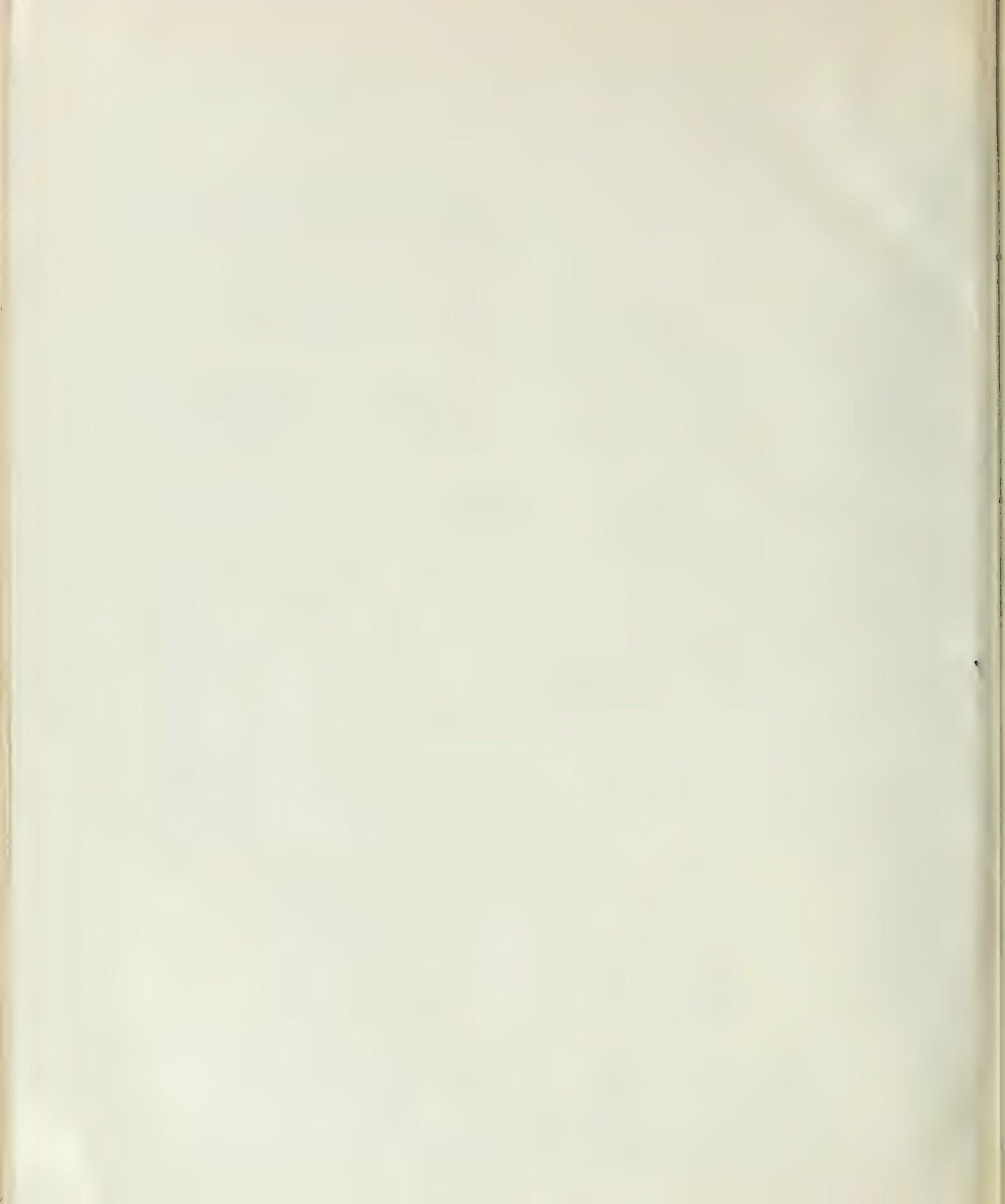
FIG. 7



FIG. 8



FIG. 9



## SUMMARY

1. Intracranial pressure changes may be measured by the application of an inverted tambour to an area of bone defect. With this recording tambour we were able to observe changes in intracranial pressure, which roughly follow absolute pressure changes in the cerebro-spinal fluid.

2. Rhythmic changes in intracranial pressure of varying types have been recorded.

3. Epileptic attacks are associated with a rise in intracranial pressure and are unaccounted for by activities of the patient. A rise of blood pressure sometimes occurs with the rise of intracranial pressure during the attacks. The patient gives subjective complaints associated with these changes.

4. Petit mal attacks show typical kymographic tracings of pressure changes.

5. Intracranial pressure is lowered by the intravenous and oral administration of hypertonic solutions. The oral administration of 200 c. c. hypertonic Ringer's gives a transient fall of 20 mm. ( $H_2O$ ) with a terminal rise of pressure. From 30 per cent hypertonic glucose given intravenously we found a prolonged fall of pressure averaging 20 mm. after a slight initial rise. These changes observed by our recording system represent far greater changes in the true intracranial pressure. Glucose is more ideal to use for therapeutic purposes.

6. The administration of hypotonic solutions (water) gives a constant increase of intracranial pressure.

7. These changes are adequately controlled by the use of isotonic solutions.

We wish to express our appreciation to Dr. Adolf Meyer, Dr. Lewis Weed, and Dr. Leslie B. Hohman for their valuable suggestions and kindly criticism in carrying out this study, and to the patient for his unusual co-operation and assistance.

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## DESCRIPTION OF PLATE

FIG. 2.—Photograph showing the application of the tambour to the patient's head, and the attachments for recording changes in pressure.

FIG. 3.—Tracing showing circulatory and respiratory variations.

FIG. 4.—Waves of third type showing transition to a quiescent period. Obtained during starvation.

FIG. 5.—Waves resembling those of gastric tonus.

FIG. 6.—Waves resembling gastric contractions.

FIG. 7.—Synchronous gastric and intracranial pressure changes showing parallel variations. Moved at M.

FIG. 8.—125-second apnea curve.

FIG. 9.—Tracing obtained during a petit mal attack.

## THE DETERMINATION OF ACETONE IN THE BREATH

By HAROLD L. HIGGINS

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For the past five years, we have been using in this clinic a chemical method of estimating quantitatively the acetone in the breath, determining in this way if acetone bodies are present in the body and roughly in what amounts. We have found this of practical value in many cases, especially in dealing with the following problems:

1. In patients with hyperpnea, when acidosis is recognized or suspected, it is important to know immediately if acetone bodies may not be the cause of the condition. Although analysis of the urine would give the desired information, there is often failure or delay in obtaining a specimen, so that the determination of their presence or absence in the breath affords an important saving of time. The time element is particularly important here, as an acetone body acidosis (except in diabetes) usually responds readily to early treatment by the administration of carbohydrates.

2. In diabetic patients, the determination of acetone in the

breath affords a rapid quantitative measurement of the amount present in the body; the determination is useful in diagnosing diabetic coma, and in following the condition of a patient when coma is impending or when changes in diet are being made.

3. In cases in which a patient has been getting little or no food, as in fasting or recurrent vomiting, the determinations of the acetone in the breath act as a guide to the patient's condition.

Quite recently Widmark<sup>1</sup> has shown that acetone passes from the blood to the alveolar air by a process of diffusion, and that the acetone content of the blood and of the alveolar air are proportional. This gives the determination of the acetone in the breath a firmer footing, as it means that the acetone in the breath is a rough index of the acetone in the blood.

<sup>1</sup> Biochem. Jour., 1920, xiv, 379.

The method we have used has been based on that of Scott-Wilson.<sup>2</sup> Hubbard<sup>3</sup> has used the Scott-Wilson reagent to determine the acetone excretion through the lungs. Hubbard's method is quite lengthy and enters into refinements in that interfering substances such as primary alcohols, aldehydes, etc., are removed. For clinical purposes, however, this is not at all necessary.

The air for the determination is collected in a rubber bag of 1000 c. c. capacity when full. A football bladder should prove satisfactory. The air may be collected in various ways. When possible, it is most satisfactory for the patient to blow up the bag as one does a toy balloon. With babies or unconscious patients, a mask and valves may be used, or the patient may breathe back and forth several times from a bag containing air, as in the Plesch method of obtaining the alveolar air. The results obtained when using alveolar air are higher approximately by twice those when valves are used; but this is unimportant for diagnosis, as the method does not have to be absolutely quantitative, and differences may be allowed for. When determinations are made with the same patient from day to day, the same method of collecting the sample is used.

If the bag is washed out with 1000 c. c. of air following a determination, practically no acetone remains in the bag to interfere with subsequent determinations.

Within 30 seconds after collecting the specimen, it is blown through the Scott-Wilson acetone reagent.<sup>4</sup> About 25 c. e. of the reagent are placed in a large test-tube (30 mm. in diameter  $\times$  200 mm. in height); a blowing tube is used similar to that in Folin's micro method for ammonia. The liter of air is blown through the solution in about 30 seconds. At first we used two tubes in series each containing the reagent, but even when large amounts of acetone were present there was only a trace of cloudiness in the second tube. If acetone is present a white cloud is formed, which reaches its maximum density in about five minutes.

A standard solution of acetone is made up and standardized (Messinger titration), containing approximately .02 mg. per cubic centimeter. In making this solution, 5 c. e. of acetone are diluted to one liter (Solution I); 5 c. e. of this solution are in turn diluted to one liter (Solution II). Solution I is fairly stable and will keep for months, but Solution II should be made fresh every two days.

To 25 c. e. of Scott-Wilson reagent in a second tube one adds, according to the amount of acetone in the air test, 1 c. c., 5 c. c., 10 c. c. or 20 c. c. of Solution II; this is done as soon as possible after the air test has been made.

Comparison of the cloud in the tubes will tell the amount of acetone present. This is made more accurately by diluting the tubes with known and unknown amounts of acetone with

<sup>2</sup> Jour. Physiol., 1911, xlii, 456.

<sup>3</sup> Jour. Biol. Chem., 1920, xliii, 57.

<sup>4</sup> Mercuric cyanide ..... 10 grams.

Sodium hydroxide ..... 180 grams.

Water ..... 1200 c. c.

The solution is shaken in a flask and 400 c. c. of a 0.7268 per cent of silver nitrate are added. This reagent will keep indefinitely, the clear fluid being decanted from the precipitate which tends to form.

water until approximately the same cloudiness is present in both; the amount of acetone in the breath is calculated from the volumes of fluid in the two tubes and the amount of acetone in the standard. A nephelometer<sup>5</sup> may be used if desired.

The amount of acetone present in one liter of air, even in cases in which there is a large amount, will give only a cloudy suspension, which makes comparison easy.

When this test is used, a normal person will show no acetone and the solution will remain clear.

.02 to .05 mg. acetone per 1000 c. c. air may be regarded as a trace.

.10 mg. per 1000 c. c. air is a moderate amount.

.20 mg. per 1000 c. c. air is a large amount.

.40 mg. per 1000 c. c. air is a very large amount.

Two determinations (duplicates) at the same time have always given practically the same results.

The following cases are of interest in showing the application of the method:

CASE A. M., boy, aged 9, admitted to the hospital on October 6 with diabetes, showing some hyperpnea and tendency to coma. The diet was limited to vegetables until October 8, when fasting was started. On October 10 he was sugar free and feeding was commenced. On October 13 he was receiving 13 gm. carbohydrate and 300 cals. On October 21 he was receiving 40 gm. carbohydrate and 1060 cals. Tolerance 100 gm. carbohydrate. The figures for acetone per liter expired air were as follows:

Oct. 6.....	.21 mg.	Oct. 9.....	.18 mg.	Oct. 16.....	.05 mg.
Oct. 7.....	.20 mg.	Oct. 10.....	.20 mg.	Oct. 18.....	.03 mg.
Oct. 8.....	.18 mg.	Oct. 13.....	.05 mg.	Oct. 21.....	.03 mg.

On October 6 the alkali reserve by the Van Slyke method was 25 vols. CO<sub>2</sub> per cent.

CASE M. F. C., aged 12, and CASE M. C., aged 16, were epileptic patients, who were treated by starvation to observe the effect on the convulsions. Acetone determinations in the breath were made in each case during the fast.

M. F. C.	M. C.
Day of fast	Day of fast
1. .03 mg.	1. .01 mg.
2. .30	2. .04
3. .44	3. .11
4. .50	4. .10
5. .70	5. .09
6. .70	6. .05
Day of feeding	Alkali reserve = 38 vols. CO <sub>2</sub> per cent (Van Slyke) on last day of fast.
1. .33	
2. .15	
3. .00	

Alkali reserve = 41 vols. CO<sub>2</sub> per cent (Van Slyke) on last day of fast.

The above is interesting in showing one patient who is very susceptible to acetone body acidosis, while the other is hardly susceptible at all.<sup>6</sup> This patient, M. F. C., shows the largest amount we have found. It is interesting to note that a high acetone in the breath does not necessarily mean a low alkali reserve (acidosis).

CASE C. B., aged 8½ months. Brought to the hospital at 9 a. m., having had approximately 20 green watery stools in the preceding 24 hours. He was drowsy, feverish, and with rapid deep respirations suggesting hyperpnea. Acetone in breath, .30 mg. per 1000 c. c. Only a trace was present 36 hours after the intravenous injection of 125 c. c. of 8 per cent glucose solution.

<sup>5</sup> Marriott, Jour. Biol. Chem., 1913, xvi, 293.

<sup>6</sup> Cf. Higgins, Peabody and Fitz, Jour. Med. Res., 1916, xxxiv, 267.

# CERTAIN CULTURAL CHARACTERISTICS OF THE GONOCOCCUS

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**1. Introduction.**—As a consequence of the studies made in this laboratory, on the effects of disinfectants on the gonococcus, using the method of cultivating the gonococcus which has been described by Swartz,<sup>1</sup> we have found it desirable to make some investigations on the cultural characteristics of this organism. The ease and certainty with which profuse growth can be obtained by this method have simplified greatly the experiments made for the above purpose.

**2. Historical.**—The desirability of the presence of uncoagulated protein in media for the gonococcus has been recognized since the day of Bumm.<sup>2</sup> Growths have been obtained on such media, placental serum,<sup>3</sup> blood serum,<sup>4</sup> ascitic fluid,<sup>5</sup> hydrocele fluid,<sup>6</sup> whole blood,<sup>7</sup> etc., being employed. Until recently, the growths have been described as scanty, and rather apt to die out upon repeated transfer. The morphology of individual colonies has been described in great detail.<sup>8</sup>

Vannod,<sup>9</sup> using a slightly alkaline medium, called attention to the necessity of careful adjustment of the reaction of the media; while Finger and others<sup>10</sup> stated that the best growth was obtained on slightly acid media. Martin,<sup>11</sup> using more accurate methods of measuring the reaction, recommended media having a reaction of pH 7.6, which is close to that of the body fluids, and claimed that the addition of body fluids to the media is of use principally as providing a buffer which regulates the reaction.

Hall<sup>12</sup> described a medium made with a watery extract, which was boiled, of beef testicles. The juice of these organs was supposed to be especially favorable to the gonococcus. Stickel and Meyer<sup>13</sup> recommended a medium rich in amino-acids and vitamines, after the principles of Cole and Lloyd.<sup>14</sup> The growths obtained with these media, however, were not much superior to those of the older investigators.

Wherry and Oliver<sup>15</sup> first called attention to the fact that the gonococcus is a microaerophile organism, and grows best at a reduced oxygen tension. They obtained profuse growths. Chapin<sup>16</sup> replaced part of the air in his culture tubes with CO<sub>2</sub>, and felt that the presence of this gas was the important factor in securing good growth. Cohen and Fleming,<sup>17</sup> and Kohman,<sup>18</sup> working with the meningococcus, found that it, too, grows better at reduced oxygen tension. Kohman<sup>19</sup> concluded from his experiments that the superior growth of the meningococcus in closed systems was due entirely to the excess of moisture present and not to a decreased oxygen tension. He found that when grown in connection with a culture of *B. subtilis*, by the method of Wherry and Oliver,<sup>15</sup> the oxygen tension was reduced 9.5 to 15.3 per cent. Gates<sup>20</sup> concluded that, when the reduction is accomplished by substitution with CO<sub>2</sub>, the beneficial

results are due to the action of CO<sub>2</sub> in changing the reaction of the media. He found that the meningococci grew equally well in atmospheres containing from 15 to 40 per cent of oxygen, that the reaction must be pH 7.4, and that the presence of sufficient moisture is necessary for luxuriant growth. Reudiger<sup>21</sup> obtained good growth by simply stoppering his tubes tightly after inoculation. It is generally agreed that the gonococcus will not grow profusely under anaerobic conditions,<sup>22</sup> and that the best growth is obtained under aërobic conditions (2-b).

Brons (1907),<sup>23</sup> investigated the sugar reactions of the gonococcus, and found that dextrose was fermented with the production of acid but not gas, while maltose, levulose, saccharose, lactose and galactose were not fermented. This has been confirmed by others.<sup>24</sup>

It has been stated that gonococci, after long subculturing, may become Gram-positive. Vannod<sup>9</sup> and Martin<sup>11</sup> found that the organism would become, after a time, habituated to plain media containing no uncoagulated protein, and give good growth upon it.

Although investigators have been generally in agreement upon certain points, there is diversity of opinion on others. Thus, the sugar reactions of the gonococcus and the morphology of its colonies, as found by different workers, are the same. On the other hand, a number of quite different reactions have been recommended as the most suitable for the growth of the gonococcus, and while all have found the organisms to grow better in closed systems, it is doubtful whether this difference is due to lowered oxygen tension, increased CO<sub>2</sub> tension, change in reaction due to CO<sub>2</sub>, or abundance of moisture. That the gonococcus should be able to accustom itself to plain media and become Gram-positive, are very important points, if true.

We have followed generally these lines in our work, also attempting to determine for the gonococcus, when grown in sugar media, an acid death-point like that described for *B. coli* by Michaelis and Marcora<sup>25</sup> and by Bruenn.<sup>26</sup>

**3. Growth on Culture Media.**—One strain of gonococcus in our series showed a very slight growth consisting of a few isolated colonies after being transplanted several times on the usual medium, and then transplanted to plain agar containing no uncoagulated protein. A second transfer produced no growth. Aside from this instance, our organisms have not grown on plain media, either when freshly isolated or after many subcultures in the laboratory.

Media made with ascitic fluid, hydrocele fluid, pleural fluid, rabbit serum, and cat cerebro-spinal fluid all showed good

growth. We may therefore conclude that the nature of the uncoagulated protein present in the media is of minor importance. The same may be said of the quantity present, since some of our samples of fluid contained two or three times as much albumin as others.

On solid media isolated colonies of the gonococcus, which occurred under unfavorable conditions of growth, such as a too high oxygen tension or the presence of small quantities of some germicidal substance, presented the same appearances as those described by Martin<sup>7</sup> and others. A translucent gray color by reflected light, changing to a fairly clear light brown by transmitted light was found by us to be characteristic. Under favorable conditions, the growth formed a fairly thick film over the entire surface of the medium, in which individual colonies could not be distinguished. The same color and translucency were retained. The growth shows a definite tendency to cohere, and is rather mucoid in nature. It comes off easily from the medium in the form of flakes. We have never seen growth in the depths after stabbing the medium.

On liquid media consisting of two-thirds beef or veal infusion bouillon and one-third ascitic or hydrocele fluid, the gonococcus grows well when the oxygen tension is lowered. The medium is not clouded, the organisms growing in a pellicle on the surface. After a time, many organisms sink to the bottom, where they remain as a granular precipitate. As a consequence of this, one often sees delicate shreds and strings of organisms hanging from the lower surface of the pellicle.

After many subcultures, some of our strains grew with less profusion on solid media and showed many involution forms. We found that, if such a strain were passed once or twice through liquid media, the original profusion of growth was restored, and the involution forms diminished.

In liquid media containing the various sugars, we found the same fermentation characteristics described by Martin,<sup>7</sup> Brons,<sup>20</sup> Rothe,<sup>21</sup> Elsee and Huntoon,<sup>22</sup> the gonococcus fermenting dextrose, with the production of acid, but not of maltose.

We have had little success with media containing no uncoagulated protein, such as those described by Cole and Lloyd,<sup>23</sup> Stickel and Meyer,<sup>24</sup> Hall,<sup>25</sup> and Clark.<sup>26</sup>

Microscopically, we have found the organisms always to be typical biscuit-shaped diplococci. In old cultures, involution forms, consisting of individual pairs larger than the average, are seen. These sometimes attain a diameter four or five times as great as that of normal cocci. Some strains seem more prone to the formation of involution forms than others. This does not, however, interfere with their vigor of growth.

None of our growths has ever shown the slightest tendency to irregularity of staining by the Gram method. Even after 20 or 30 subcultures, we have never seen any Gram-positive forms.

*4. Oxygen Tension.*—We have confirmed the results of previous workers as to the necessity of a reduced oxygen tension. It is immaterial whether this is obtained by exhausting part of the air, or by replacing it with CO<sub>2</sub>. Using the

method of Swartz,<sup>1\*</sup> in which the pressure in the tube is reduced 7 to 10 per cent by first heating and then stoppering so as to make the tube air-tight, we have obtained very profuse growths on ascitic-fluid veal infusion agar. In desiccators from which part of the air is exhausted, we have observed good growth up to a 40 per cent exhaustion. The exact limits of pressure which will permit growth have not been determined. The growths at a 10 per cent reduction are luxuriant and not surpassed by those at any other pressure used by us. If, for any reason, the system is not closed, and atmospheric pressure obtains in the culture tube, the growths are always very strikingly reduced and sometimes do not appear at all. This is well shown in Fig. 1, *A* and *B*. The two tubes are from the same batch of media and were inoculated from the same vigorously growing culture. That in which the oxygen tension was reduced showed luxuriant growth, the other only a few colonies.

*5. Reaction.*—The usual media used by us had a reaction of pH 7.4. In order to determine the effect on growth of the initial reaction of the medium, a series of tubes was prepared, in which the usual medium (ascitic fluid veal infusion agar) was titrated, N/10 Na OH and N/10 HCl, and suitable indicators being employed, to a number of different reactions, both acid and alkaline. The indicators used, having no germicidal action, were allowed to remain in the medium, which after

\* Briefly, the method is as follows: The medium employed is a 2 per cent beef or veal infusion agar, prepared in quite the ordinary manner, which is brought to a reaction of pH 7.6, phenolsulphonphthalein being used as an indicator. After autoclaving, the reaction having come to about pH 7.4, sterile ascitic, pleuritic or hydrocele fluid is added to the melted agar in the proportion of one part of fluid to two parts of agar. The tubes are then sealed with sterile rubber stoppers and slanted. This corking prevents evaporation, permits the medium to be kept in the incubator, facilitates the detection of any contamination and keeps the medium warm for inoculation at any time. The use of the rubber stopper has a further advantage in that it prevents contamination much more surely than the ordinary cotton stopper.

Inoculation is made as plentifully as possible. It is important to have the medium at body temperature when the inoculation is made, to keep it so thereafter, and to prevent cooling of the material before inoculation. Immediately after inoculation, the tube, held horizontally, is turned so that the agar slant is uppermost. Held by the butt, it is then passed longitudinally through the Bunsen flame about three or four times and quickly corked. Experiments with suitable apparatus show that this procedure keeps the air in the test-tube sufficiently to cause the pressure within to be lowered from 70 to 100 mm. of mercury (about 10 per cent of atmospheric pressure), when the tube is again cooled to 37.5° C. By this procedure the medium is not coagulated nor the gonococci harmed. By following this simple technique, we obtain with perfect regularity viable colonies in from 15 to 18 hours with profuse growth in 24 hours. The viability of the gonococcus on this medium is about 7 days. If other organisms are found to be present, plates may be made from the same medium and placed in the incubator in vacuum desiccators, in which the pressure has been lowered 10 per cent. Good growth may be obtained on fluid media prepared as above, except for the agar, and with or without sugar. The agar tubes should have, after hardening, a small quantity, about 0.5 c.c. of water of condensation in the lower angle of the slant. This assures the best growth.

titration was slanted and cooled. This insured that no change of reaction took place on cooling or later. The tubes were then inoculated from the same vigorously growing culture and cultivated at reduced oxygen tension in the usual manner. The results of such a series are shown in Table 1.

TABLE 1.—INITIAL pH OF MEDIA

Gonococcus	5.4	5.6	6.0	6.6	7.0	7.6	8.0	8.6	9.0
24-hour reading.....	0	0	0	+	+	+	+	0	0
48-hour reading.....	0	0	0	+	+	+	+	0	0
7-day reading.....	0	0	0	+	+	+	+	0	0

The tubes at pH 6.6 and pH 8.0 showed growths perhaps slightly less luxuriant than the rest, but among the others no distinction could be made. Other conditions being favorable, then, there is a fairly wide range within which the initial reaction of the culture medium does not affect the growth of the gonococcus.

Other experiments were made, in which emulsions of gonococci were exposed to solutions of varying reactions for periods of 20 minutes, and then cultured on the usual media.<sup>25</sup> They are able to resist for this length of time the action of solutions from pH 4.5 to pH 8.5 inclusive, but an acid solution of pH 4.0 or an alkaline solution of pH 9.6 will kill them in 20 minutes.

6. *Moisture*.—We found that the presence of moisture in the culture media is desirable and indeed necessary for profuse growth. Tubes of culture media, stoppered with cotton and placed in the incubator, were allowed to dry until the medium cracked and no "water of condensation" remained. These tubes were then inoculated from a vigorously growing culture, stoppered, and cultivated at reduced oxygen tension in the usual manner. No growth occurred. Suitable controls showed the gonococci used to be viable. Several days later, the corks were removed from these tubes, sterile ascitic fluid was added until there was about 1 c. c. excess in the lower angle of the slant, and they were reinoculated and cultivated as before. Luxuriant growth took place. This experiment merely confirmed our observations over a long period of gonococcus cultivation, during which dried-out media always gave inferior growth.

That moisture alone, in the absence of reduced oxygen tension, will not give luxuriant growth, was proved in the following manner: Several tubes were inoculated from a vigorously growing culture. Half of them were stoppered with cotton, and placed in a large desiccator, the bottom of which was covered with a layer of water containing some half-immersed gauze to provide a large surface of evaporation. The entire desiccator was placed in the incubator without altering the atmospheric pressure within. This arrangement prevented any drying of the media, and maintained the water-vapor tension of the air at a high point. The remaining tubes were stoppered and cultivated at reduced oxygen tension in the usual manner. In all the stoppered tubes profuse growth occurred in 24 hours, while in those in the desiccator only a

very few colonies appeared in 48 hours, the contrast being very striking. After 48 hours, one of the tubes from the desiccator was heated, stoppered and cultivated in the usual manner. Numerous colonies appeared in 24 hours, showing that although the gonococci were present and alive, their growth, even in the presence of abundant moisture, had been inhibited by a too high oxygen tension.



FIG. 1.—A, 24-hour growth gonococcus in reduced atmospheric tension. B, 24-hour growth, same strain gonococcus on same medium, at ordinary atmospheric tension.

The experiments described in paragraphs 4, 5 and 6 seem to us to prove conclusively that the most important factor in the profuse growth of gonococcus in closed systems is reduced oxygen tension. It cannot be the presence of CO<sub>2</sub>, since in our work the reduction of pressure has been attained by simply removing part of the air. This too would eliminate any change in the reaction of the media, due to the presence of an excess of CO<sub>2</sub>, and in addition the experiments described in paragraph 5 show beyond dispute that small changes in the reaction

of the medium are a matter of indifference in the initial growth of the gonococcus. The presence or absence of moisture will not determine a profuse growth if the oxygen tension is not lowered. We may conclude, therefore, that the original deduction of Wherry and Oliver,<sup>12</sup> that the gonococcus is a micro-aerophile organism, and that a reduced oxygen tension is essential to its best growth, is correct.

*7. Changes in Reaction on Growth.*—In order to determine the acid death point for the gonococcus, cultures were made in liquid media containing 1, 2 or 3 per cent dextrose. Our experience showed that after ten days' incubation all growth had ceased, and that there were no more living organisms. Hence, after the tubes had been left for at least ten days in the incubator, the acidity of the media was tested colorimetrically and electrometrically.

The "acid death-point" by this method for gonococci grown in dextrose ascitic fluid bouillon is pH 5.6, the variations mentioned in the quantity of dextrose present making no difference.

The gonococcus always produces acid when grown on our ordinary ascitic or hydrocele fluid beef or veal infusion agar, the final pH being 6.2. This medium is not especially rendered sugar-free, but contains no reducing substance for Fehling's solution.

#### CONCLUSIONS

1. The superior growth of gonococcus in closed systems, when part of the air or of the oxygen has been removed or replaced, is essentially due to the lowered oxygen tension, and not to moisture, change of reaction, or presence of CO<sub>2</sub>.

2. Moisture is however necessary to good growth.

3. A reduction in the oxygen tension of 10 per cent is sufficient to produce optimal growth.

4. The gonococcus will grow luxuriantly, if the oxygen tension is suitable and moisture and uncoagulated proteid are present, on media having an initial reaction anywhere between pH 6.6 and pH 8.0 inclusive.

5. In dextrose-containing media, the acid end-point for the gonococcus is pH 5.6.

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## A LABORATORY METHOD FOR THE PREPARATION OF FIBRINOGEN<sup>1</sup>

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An exasperating difficulty is frequently encountered in preparing fibrinogen by the method which employs sodium chloride to salt it out of solution. This difficulty is the insolubility of the final precipitate of fibrinogen in dilute sodium chloride solution, a condition that renders it useless for experimental purposes.

In this method the first precipitate of fibrinogen usually dissolves without difficulty in a 1 per cent solution of sodium chloride. The second precipitate, frequently a tough membrane-like flake, sometimes fails to dissolve, even after stirring with a glass rod for 30 minutes or longer. When the second precipitation does dissolve, it is difficult to purify it by another precipitation, as the third precipitate is very frequently insoluble.

By substituting, at Dr. Howell's suggestion, ammonium sulphate for sodium chloride to salt out the fibrinogen a readily soluble precipitated fibrinogen was secured. No difficulty has been encountered in dissolving fibrinogen which has been re-precipitated three times. Thus a fibrinogen free from prothrombin, which tends to adhere to the precipitate, may be obtained.

A concentration of ammonium sulphate in the plasma adequate to cause complete precipitation of the fibrinogen for physiological purposes and not of the other plasma proteins was found to be one part of saturated ammonium sulphate solution to four parts of oxalated plasma. Concentrations above this bring down some of the paraglobulin. To determine this fact fibrinogen was precipitated from five equal volumes of plasma drawn at the same time from one dog. In four of the tubes saturated ammonium sulphate solution was added, giving final concentrations of the salt in the plasma of 16, 20, 23 and 26 per cent. In the fifth tube of plasma precipitation was caused by sodium chloride, one part of the saturated solution to one part of plasma. The concentration of one part saturated ammonium sulphate to four parts of plasma brings down practically all of the fibrinogen. The solutions of fibrinogen secured from the above precipitates were filtered and the filtrates heated slowly in a water bath to just 60 degrees in order to coagulate the fibrinogen. The contents of all the tubes were then filtered and the filtrates were heated up to 85 degrees. The solutions of proteins precipitated by a concentration of ammonium sulphate greater than 20 per cent became distinctly opalescent, demonstrating the presence of paraglobulin. The solutions of protein precipitated by ammonium sulphate in concentration of 20 per cent or 16 per cent, and by sodium chloride in concentration of 50 per cent,

remained clear or developed sometimes but the slightest opalescence. As the concentration of one part of saturated ammonium sulphate to four parts of oxalated plasma brought down as much fibrinogen as the sodium chloride method and did not practically contain any paraglobulin this concentration was selected as being adequate.

The details of the preparation of fibrinogen by the use of ammonium sulphate as a precipitant are:

1. Use cat's or dog's blood, oxalated and centrifugalized for 20 minutes. Carefully pour or pipette off the clear plasma.

2. Add to the plasma one-fourth of its volume of saturated solution of ammonium sulphate. Centrifugalize the precipitate promptly for five minutes. Pour off the supernatant fluid. Carefully wash the precipitate at least twice by layering over it one-fifth saturated solution of ammonium sulphate. Add to the washed precipitate a volume of 2 per cent sodium chloride equal to that of the original plasma and stir gently with a glass rod until dissolved. Filter the solution.

3. Precipitate the solution by adding one-fourth of its volume of saturated ammonium sulphate solution. Centrifugalize promptly for five minutes. Pour off the supernatant liquid and drain. Wash for some minutes in one-fifth saturated solution of ammonium sulphate and drain. Wipe the inside of the glass centrifuge tube with filter paper. Dissolve in 1 per cent sodium chloride solution and filter. This process may be repeated a third time but usually two precipitations suffice.

The solution should clot in a few minutes on the addition of thrombin or prothrombin and calcium, and should not clot in 24 hours either spontaneously or on the addition of calcium chloride.

Fibrinogen prepared by using sodium chloride has time and again failed to go into solution, whereas fibrinogen prepared from the same plasma, but precipitated with ammonium sulphate, dissolved rapidly.

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<sup>1</sup> Work done under the tenure of the Le Conte Memorial Fellowship of the University of California, 1918-1919.

# RESTORATION OF HEARING IN A CASE OF GUNSHOT INJURY OF THE EUSTACHIAN TUBES

By JOHN W. BAYLOR

(From the Department of Surgery, The Johns Hopkins University and Hospital)

Many of the technical difficulties of an examination of the ear, nose and throat have been removed by the introduction of electrically lighted instruments. The nasopharyngoscope, devised by Dr. Edgar M. Holmes of Boston, is especially valuable for the diagnosis of infections of the posterior ethmoidal and sphenoidal sinuses, and for the inspection and treatment of the Eustachian tubes. It is true that the use of the nasopharyngoscope is not essential for the diagnosis and treatment of the majority of cases, and it is only by constant practice that one acquires sufficient skill to use it to advantage in the cases that could not be treated by the ordinary methods. For the past five years we have used this instrument in the examination of all nose and throat cases and in the treatment of all Eustachian tube conditions, and it is to this fact that we ascribe the successful outcome in the following case:

F. N., white, aged 28. Surgical Nos. 50309 and 50448, Medical No. 43470.

The patient was admitted to The Johns Hopkins Hospital February 20, 1920, complaining of deafness in both ears that had resulted from gunshot wound received two years before. The bullet from a 38 caliber pistol had entered the right side of his face 1 cm. in front of the tragus at the lower border of the zygoma, and passed downward at an angle of about 35 degrees. He developed a temporary facial palsy and a subjective hemianesthesia, both on the right side. Immediately after the accident he was confined to bed for three weeks in a hospital in Tennessee. No attempt was made to remove the bullet. His hearing was subjectively normal during this period. A short time later he noticed some impairment of hearing in the right ear, and in six or seven months this had progressed to almost complete deafness. There was a discharge from the left ear for two or three months. This did not appear until four weeks after the injury and was not associated with earache. Hearing gradually became impaired on this side also, but to a lesser degree than on the right.

On admission, there is no discharge from either ear. The drums are retracted and thickened.

## HEARING TESTS

### RIGHT EAR

Loud shouts heard but not understood (a Bárány Lärmaparát employed).

Bone conduction is lengthened on both sides.

Vestibular tests are normal.

The naso-pharynx is filled with scar tissue. The pharyngeal orifices of the Eustachian tubes and the fossæ of Rosenmüller are not recognizable.

From the history of the onset of deafness, the appearance of the naso-pharynx, and from the X-ray localization, it is apparent that the bullet passed through the naso-pharynx and injured both Eustachian tubes.

The plan of treatment was to excise the scar tissue in the naso-pharynx and, after the wound had healed, to locate the orifices of the Eustachian tubes with the aid of an electric nasopharyngoscope and to try and restore their patency by dilatation and inflation.

### LEFT EAR

Whispers not heard. Conversational tone understood at a distance of 12 inches.

On February 24, 1920, the patient was anesthetized and placed in the Trendelenburg position. The soft palate was retracted by means of small rubber catheters passed through each nostril and brought out through the mouth.<sup>1</sup>

The tissues of the naso-pharynx were infiltrated with procaine and adrenalin in order to control bleeding partially, and to diminish the reflexes that invariably occur during operative procedures in the naso-pharynx.<sup>2</sup>

Even under direct vision the orifices of the Eustachian tubes could not be recognized. The scar tissue was removed by sharp dissection and with sharp nasal rongeurs. The bleeding was controlled wherever possible by the introduction of catgut sutures. The naso-pharynx was not packed.

The post-operative course was uneventful until the fifth day when a bronchopneumonia developed on the right side. The patient was transferred to the medical service where he remained until March 28, 1920, at which time he had completely recovered. Nothing was done to the naso-pharynx during this period with the exception of frequent irrigations with sterile normal salt solution, followed by the introduction of sterile albolene into each nostril.

During the next three months about three hours a week were devoted to the localization and dilatation of the Eustachian tubes.<sup>3</sup>

<sup>1</sup> Ether anesthesia was given through the mouth-gag used for tonsillectomies. A good illustration of it is to be found in an article by Crowe, Watkins and Rothholz in The Johns Hopkins Hospital Bulletin, 1918, XXVIII, p. 18, Fig. 9.

<sup>2</sup> When adenoids are removed even under light ether anesthesia there is almost invariably an interruption of the respiratory rhythm. We have had one death due to spasmotic closure of the glottis and to arrested heart action, presumably caused by stimulation of the vagus. This occurred during the removal of a large metallic foreign body that had been present in the naso-pharynx of a child for several months.

<sup>3</sup> For several years we have used the electric nasopharyngoscope for the introduction of the catheter and the dilatation of strictures of the Eustachian tube. If sufficient time is devoted to the anesthetization of the nose, naso-pharynx and the Eustachian tubes, the entire procedure may be carried out with but very little discomfort to the patient.

The floor of the nose, the lower border of the inferior turbinate and the naso-pharynx on each side are cocainized. For this purpose we prefer to use a small piece of cotton on an applicator, with a 20 per cent solution of cocaine, rather than to use a weaker solution in a spray. If the excess of cocaine is removed by pressing the cotton between two layers of gauze there is no danger of poisoning in this method of anesthetization.

The nasopharyngoscope is then introduced along the floor of the nose on one side, and the Eustachian applicator, moistened with a 20 per cent solution of cocaine, is passed through the other nostril and into the orifice of the Eustachian tube. If left in place for five minutes, the Eustachian tube will be sufficiently anesthetized to permit the catheterization and subsequent passage of bougies without pain.

The catheters and the soft rubber ear syringe used for inflation are sterilized by boiling. The whalebone bougies are placed in a 1:1000 solution of bichloride of mercury and are allowed to remain for 15 minutes. The tip of the bougie is dipped into sterile olive oil or vaseline in order to render its passage along the Eustachian tube less irritating.

Even with the magnification and the brilliant illumination of the naso-pharynx that is obtained by the use of the naso-pharyngoscope, it was extremely difficult to find the orifices of the Eustachian tubes.

On the left side there was no Eustachian cushion and for many days we were unable to localize the orifice of the tube. On one occasion, however, a small plug of mucus was seen to be forced out of a minute opening during the act of swallowing. The smallest sized catheter was then placed directly over this area and by inflation and the use of the diagnostic tube it was demonstrated that this small opening led into the Eustachian tube. Immediately following this first inflation there was marked improvement in hearing on the left side. It is noteworthy that the improvement was permanent and the deafness did not return in two or three days, as is usual in chronic inflammatory conditions of the Eustachian tube.

On the right side the Eustachian cushion was present, but attempts to inflate and to pass bougies indicated that the tube had been divided a few millimeters above the pharyngeal orifice. The pinpoint opening of the tube was located only after many hours of observation, probing, and attempts to inflate. Once the opening was located, however, inflations and dilatations with whalebone bougies rapidly restored the hearing. From attempts to pass bougies it was apparent that there was a further stricture

higher up the tube. This was probably due to the fact that the bullet had entered the right side and caused more extensive damage to the right tube than to the one on the left.

After three months of treatment the patient is able to hear from the balcony of a theatre for the first time since the accident. Ordinary conversation can be heard from any part of the room. A low tone tuning-fork, C<sub>128</sub>, can be heard by air conduction on both sides. Air conduction and bone conduction are about equal in the left ear (June 21, 1920). The hearing in the right ear still remains slightly impaired and bone conduction is a little better than air conduction.

With this improvement in hearing there has been no appreciable change in the appearance of the tympanic membrane on either side.

It is possible that the scar-tissue will ultimately contract and again produce stenosis, but subsequent treatments should not be more difficult than in ordinary strictures of the Eustachian tube. The point we wish to emphasize is that it would have been impossible to have benefited this patient in any way without the use of the electrically lighted nasopharyngoscope.

## THE HISTOLOGICAL PATHOLOGY OF A CASE OF MEASLES CONJUNCTIVITIS

By JOHN R. PAUL

(From the Department of Pathology, The Johns Hopkins University)

Despite the great importance of measles and our increasing familiarity with the serious proportions which the complications of this disease may assume, our knowledge of its pathological anatomy is quite limited. The most specific and in fact practically the only typical lesions which have been investigated are those which appear on the skin and buccal mucosa. Various workers have described these lesions, among whom may be mentioned Von Jürgenson<sup>1</sup> and Ewing.<sup>2</sup> Quite recently Mallory<sup>3</sup> has made a histological investigation of the development of the skin eruption in measles and of the Koplik spots, by studying serial sections of these lesions excised from patients at various stages of the disease.

A great deal of attention has been brought to bear on the more serious complications of measles, especially the pneumonia. Detailed accounts of the pathological anatomy can be found in the studies of Steinhäus,<sup>4</sup> Hecht,<sup>5</sup> MacCallum<sup>6</sup> and others.

Thus far, however, the conjunctivitis of measles has not been of more than passing interest. Classified by ophthalmologists under the general heading of exanthematos conjunctivitis, it is regarded as being practically similar in all respects to the simple forms of acute catarrhal conjunctivitis with no particular specific features (Fuchs).<sup>7</sup> Despite its mild and non-specific character, however, it is generally considered to be due primarily to the actual causative agent of measles, and in that respect it is important. From a pathological standpoint it has received very little attention, in all probability because of the mild and transient nature of the conjunctivitis, and partly

also of the difficulty in obtaining satisfactory material for study. The literature seems to contain very few descriptions of the histological pathology of specimens of measles conjunctivitis. Stargardt<sup>8</sup> speaks of one specimen in connection with a list of allied conjunctivitides, without giving any adequate description; six specimens are reported by Frosche,<sup>9</sup> who similarly makes no mention of their specific characteristics.

The material investigated in this instance was obtained from a case of measles which was under observation in the Harriet Lane Home for Invalid Children from March 29-31, 1920.

The patient, a male colored baby only two months old, had probably been premature, weighing only four pounds at birth. He had been breast fed until two weeks before admission to the hospital. Breast feedings had been stopped when, at this time, the mother suddenly became ill, developing a sore throat, fever and a marked rash. A diagnosis of measles was made and the child was immediately isolated from the mother. He did not do well on artificial feedings and 11 days after isolation from the mother also developed fever and a reddish maculo-papular skin eruption; this was accompanied by profuse running from the eyes and nose. On the following day signs of pneumonia were noted in the chest. The temperature remained elevated and the leukocyte count was 8,400. The child died on the third day after the appearance of the rash.

The body was given to the State Anatomical Board for disposal and a complete autopsy was performed 18 hours after the child's death.

The body showed a fair degree of nourishment. Over the skin there was a well defined macular rash especially prominent over the face, chest and back. The eyes showed injection of both bulbar and palpebral conjunctivæ and there was marked edema of the lids. No Koplik spots were observed on the buccal mucosa at the time of autopsy. A small amount of fluid was encountered in both pleural cavities from which a pure culture of *B. influenzae* was obtained. The lungs showed bronchopneumonia with bilateral involvement of the lower lobes. The smaller bronchi were found to be plugged with a thick muco-purulent exudate surrounded by small isolated areas of consolidated peribronchial alveoli. Cultures of *Diplococcus pneumoniae* and *B. influenzae* were obtained from the lungs, and the former was also grown from a heart's blood culture taken at the time of autopsy. The other organs did not show any gross changes apart from incidental findings, with no direct bearing on the case. These included a slight congenital stricture of the left ureter and an organizing and ossifying subperiosteal hematoma of one of the parietal bones of the skull.

The material for histological study was fixed in Zenker-formol solution; paraffin sections were cut and stained with hæmatoxylin and eosin.

The lung sections showed a typical early, but not extensive, interstitial bronchopneumonia. Sections of the liver and thymus gland showed areas of focal necrosis. Sections through some of the skin lesions revealed changes which for the most part were of a minor character. Principally they amounted to localized areas of vacuolization of the epidermal epithelium and a scanty infiltration of wandering and small round cells into the corium which largely tended to be perivascular in distribution.

For the study of the conjunctiva, sections of both upper eyelids were used, stained with hæmatoxylin and eosin, Van Gieson's, Leishmann's and bacterial stains.

In summarizing the changes found in the eyelid a review of the normal appearance of this structure may be useful. The normal histological picture of the eyelid is divided by anatomists into five layers, which from without inwards include: (1) Skin, (2) subcutaneous tissue, (3) muscular layer (*M. orbicularis oculi*), (4) tarso-fascial layer, which includes the tarsal plate, composed of dense fibrous tissue, and lodges the Meibomian glands, (5) conjunctiva.

Here we shall deal more especially with the conjunctiva and the tissue lying directly beneath it. The former is generally divided into two parts, the tarsal conjunctiva and the conjunctiva fornici. Over the tarsus it is tightly adherent to the underlying fibrous plate presenting a smooth flat surface. Above the upper border of the fibrous plate, it becomes the conjunctiva fornici. Here the surface is elevated into large folds, and beneath it there is loose fibro-elastic tissue. The conjunctival epithelium itself is pseudo-stratified in type. Beginning at the free edge of the eyelid we have a transition of the epidermis into conjunctival epithelium, the latter consisting approximately of two layers, a top layer of cylindrical cells and a deeper layer of smaller rounder cells. This regu-

larity is not, however, constant; for we have in the tarsal conjunctiva low but genuine papillæ, which consist of slight elevations with vessels and surrounding stroma, between which the epithelium dips. On the apex of the papillary prominences the epithelium retains its regular two-layered form, but in order to maintain a flat surface, between them, other cells appear in the depressions so that here several layers are produced. This continues up to the convex border of the tarsus, where not only are the papillæ higher but the surface of the epithelium dips down between them, forming sulci. With the increase in the size of these folds in the conjunctiva fornici the invaginations often assume greater proportions, appearing in some instances like tubular glands commonly described as Henle's glands.

Below the epithelium, a well defined tunica propria is present, beneath which are many lymphatic spaces and small vessels. We also find many small nests of alveolar glands partly along the convex border of the tarsus and partly in the fornix—Krause's glands, probably performing the function of accessory tear glands. Owing to the exposed situation of the conjunctiva, signs of low-grade inflammation are a constant finding in the subepithelial tissues. After the first four to six weeks of life a thin layer of infiltrating lymphatic and wandering cells appears below the stratum proprium. This layer is thickest in the receding portion of the conjunctiva fornici, where collections of lymphocytes appear often as cell nests but not true lymph follicles. These infiltrating cells extend just below the epithelium as a thin tapering line which ends before reaching the free edge of the lid.

The conjunctiva is exposed to external influences more than any other mucous membrane in the body (Fuchs).<sup>7</sup> This then is probably the cause of the variations in number and activity of the reacting cells that underly the epithelium—namely, the plasma cells and lymphocytes which are present in any healthy conjunctiva, but which are subject to variations. The size of the papilla and the adenoid structure of the conjunctiva also probably stand in relationship to the amount of irritation which has been present, for in various types of mild conjunctival inflammations we see increasing surface irregularities, new formation of Henle's glands and even cyst-like formations (Mayou).<sup>10</sup> The fact remains, however, that in the normal eyelid there are great individual variations and a line between physiological and pathological states cannot be sharply drawn. In the present instance the sections which are under investigation do not show changes that differ in any marked degree from the normal picture, but most of the factors which we commonly recognize as signs of reaction to an abnormal amount of irritation are prominent or increased.

The changes seen in these sections can be briefly summarized as: The œdematous appearance of the lid in general, dilatation of the Meibomian glands, epithelial degeneration and subepithelial reaction. The œdema of the eyelid is characterized in the section by a general looseness of structure and a loss of the compact appearance seen in normal sections. The lids show a definite increase in width, produced especially by the widening of the loose areolar and muscular tissue between the

tarsal plates and the skin. Here and there the presence of fluid, in the form of granular debris, can be detected among the loose connective-tissue fibrilla.

The widely dilated lumina of the Meibomian glands are prominent. Most of the different acini contain mucous secretion appearing in the section as a rather granular reticulum.

More definite, however, is the presence of epithelial degeneration. Some of it is unquestionably part of a post-mortem process, but this is not sufficient to mask materially the other changes. In general, the conjunctival surface is more irregular; the papillæ are very prominent and the increase of interpapillary invaginations causes the epithelium to appear as if it were almost universally stratified and consisted of more than the usual two cells in thickness. The smooth outer edge of the conjunctival epithelium is replaced by a very irregular one. Along it, quantities of desquamating cells are seen, some wholly and others partly detached, while as a rule nearly all of the outer cells are losing their compact arrangement and are tending to separate from one another, leaving intercellular spaces. In some instances, especially near the free edge of the lid, groups of superficial cells are partially dissected away from the lower layer, leaving large clear spaces beneath them which contain either coagulated fluid or often groups of necrotic wandering and epithelial cells. The inner layer of epithelium shows beginning cellular degeneration here and there, with darkening of the nuclei and changes in the cytoplasm, which for the most part consist of the appearance of small clear vacuoles about the cell nuclei. In and about these areas of epithelial degeneration there are a few wandering cells, most of which show small dark pyknotic nuclei.

It is interesting to note that the stratified epithelium of the adjacent Meibomian glands shows changes somewhat similar to those seen in the conjunctiva. The glandular epithelium is in an infinitely better state of preservation, but again there are localized areas in which the cells show vacuolization of their cytoplasm with eccentric, shrunken, or contracted nuclei. In other areas there is mucoid degeneration of the epithelial cells. Wandering cells are apparently not attracted by these areas of degeneration of the glandular epithelium and there is a noticeable absence of any submucous cellular reaction comparable with that seen beneath the conjunctiva.

The accessory tear glands of the conjunctiva forniciis, whose epithelium more nearly approaches the conjunctival type, also show changes. Colloid-like material and leucocytes are seen in many of the lumina of the branching tubular glands. Changes of the actual epithelium are scarce, but there is some vacuolization of the cells and many contain large round granules or droplets of varying size. These seem to be frequent in the more remote portions of the gland. There is a distinct reaction of infiltrating cells in the subepithelial layers in contrast to its absence in association with the Meibomian glands. In this connection, however, it is well to emphasize the fact that here the tissue is of an extremely loose nature, whereas the Meibomian glands offer practically no loose peri-epithelial spaces and are tightly enclosed in dense fibrous tissue.

In the subconjunctival tissues the presence of a reaction of wandering cells is definitely seen. As mentioned above, nor-

mally there is a compact layer of lymphoid and wandering cells distributed beneath the surface epithelium. The appearance of these underlying cells is, however, unlike the normal picture. Between the tarsal conjunctiva and its underlying fibrous plate the infiltrating cells do not seem to be particularly increased in number, but instead of a thin even layer of cells, sharply limited to the tissue directly underlying the epithelium, the reacting cells here seem to be more diffusely scattered, penetrating slightly into the outlying layers of the tarsal plate and extending occasionally through the membrana propria, masking somewhat the line of demarcation between epithelial and subepithelial tissues. Most of the infiltrating cells are large wandering cells with distinctly irregular but not lobulated nuclei. There is a conspicuous absence of polymorphonuclear leukocytes in the reaction, but with the wandering cells there are a few small round cells and an occasional eosinophile.

As regards the distribution of these infiltrating leukocytes, in the tarsal conjunctiva it cannot be said that they follow any definite rule. No perivascular grouping is demonstrable here, the cells occupy the limited area of loose submucous space and the prominent papillæ diffusely. The picture in the other portion of the conjunctiva is similar, but the presence of infiltrating wandering cells is encountered much deeper in the looser underlying tissue. The large wandering cells here seem to be more definitely in association with the small vessels. Small irregular groups consisting of a dozen or more cells are occasionally seen around one of the underlying capillaries. As a rule, these cells are younger than those described beneath the tarsal conjunctiva and more perfect, appearing as beautiful large oval cells with round nuclei, eccentrically placed.

Signs of cell proliferation are not conspicuous. A careful search for mitotic figures among not only the reacting cells but also the epithelial cells revealed only a very few in each section. Most of these were found among the leukocytes beneath the glands of the conjunctiva forniciis.

One noticeable feature about the reacting cells, however, is the large number of isolated necrotic cells. These are seen in all stages, from cells showing darkened nuclei to others in which the nucleus has become densely pyknotic, contracted and shrunken. Many show various stages of nuclear fragmentation and karyorrhexis, so that small pyknotic masses of nuclear material, for the most part round but differing in size from that of a small coccus to a red cell, are seen scattered in close association with living infiltrating cells, especially near the free edge of the lid. Groups of these cell fragments are seen within the bodies of large phagocytic cells, often filling them completely and presenting a mulberry-like appearance. This type of necrosis is perhaps the most characteristic feature presented by the section.

As a whole, therefore, the histological picture seems to be that of a diffuse type of injury to the surface, and to a lesser degree, to the glandular epithelium, calling forth a reaction in the subepithelial spaces of endothelial leucocytes which are prone to undergo necrosis easily.

The relation of bacteria to conjunctivitis of this type is not fully appreciated, but the consensus of opinion is that the

organisms which have thus far been described as occurring in the conjunctivitis of measles play the rôle of secondary invaders. Staphylococci are frequently cultured and also Streptococci (Schottelius).<sup>12</sup>

No cultures were taken from the conjunctiva of this case. Sections, however, were stained to show bacteria in the tissues by MacCallum's method.<sup>13</sup> These show large numbers of organisms along the surface epithelium. They are present for the most part upon the lower half or more exposed portion of the conjunctiva. Diplococci predominate but many appear in short chains and often in well defined clumps among the surface irregularities and superficial intercellular spaces. Occasionally they are seen within the cytoplasm of exposed dying or desquamating epithelial cells; they do not, however, seem to penetrate deeper into the tissue and a careful search through the subepithelial layers does not show any demonstrable bacteria. Those present on the surface probably play the rôle of secondary invaders and some of them unquestionably represent a post-mortem growth.

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## LYMPHOSARCOMA, LYMPHATIC LEUKÆMIA, LEUKOSARCOMA, HODGKIN'S DISEASE

By L. T. WEBSTER

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The purpose of this communication is to summarize a study of 123 cases of lymphosarcoma, lymphatic leukæmia, leukosarcoma and Hodgkin's disease. Complete histories, autopsy protocols, and charts, with a concise review of the literature, will be published in The Johns Hopkins Hospital Reports for 1921. It is sufficient here to comment upon the present status of the above conditions, outline results obtained in the survey of each group, and propose a more simple classification.

To-day, under the term "lymphatic leukæmia," it is customary to include all cases with a permanent increase in the lymphocytes of the blood associated with a hyperplasia of the lymphoid tissue. Cases of general glandular enlargement, infiltration of parenchymatous organs and bone marrow, but no clinical blood changes (pseudoleukæmia) as well as cases of leukæmia with an invasive tumor (leukosarcoma), are usually wedged into this group. "Lymphosarcoma" has so far lost the meaning assigned to it by Kundrat, that it seems to include everything from his strictly localized invasive tumor to such a case as has been recently described by Schnyder. The patient was a white male, aged 17 years, who three weeks before death, developed pains in his back, dyspnoea, and weakness. The blood count showed a leukocytosis of 12,300 with polymorphonuclears 69 per cent and lymphocytes 13 per cent. Autopsy showed an invasive tumor of the mediastinum and pleura with involvement of lymph glands, adrenals, kidneys,

liver, gall-bladder, dura mater, femur, tonsils and tongue follicles. "Hodgkin's disease" is usually considered to be an entity. But the ever increasing "intermediate forms and transitional stages" between lymphatic leukæmia and lymphosarcoma and between lymphosarcoma and Hodgkin's disease, augment beyond reason the power of the personal equation.

#### LYMPHOSARCOMA

Ten cases from the autopsy records of The Johns Hopkins Hospital may be grouped according to the location of the primary tumor. Those starting in the intestines, six in number, presented several points worthy of mention. (1) The disease tends to occur in young individuals. (2) The disease runs a rapid course, usually within one year. (3) Abdominal discomfort, loss of weight and malaise, are characteristic symptoms and abdominal tumor masses may be noted clinically. (4) At autopsy the findings are surprisingly similar. Single or multiple tumors of the small intestine (five cases) or of the mesenteric glands (one case) are encountered. These tumors spread locally to infiltrate retroperitoneal tissues, glands, adrenals, pancreas, etc. But further extension to the spleen, liver and kidneys, lymph glands, deep and superficial, testicles and bone marrow, which occurs so characteristically, must take place by way of the blood stream. Another point of predilection for this tumor formation seems to be in the glands

of the mediastinum but this series, also (four cases) is small for statistical study. Similarity to the abdominal group, however, as regards mode of extension, is striking. The tumor may be strictly localized or may spread progressively by way of the blood stream.

#### LYMPHATIC LEUKÆMIA

In the study of 15 cases of lymphatic leukæmia, three showed at autopsy hyperplastic changes in the lymphoid tissue. Clinically, however, the blood could not definitely be termed leukæmic, although the morphology and relative number of the lymphocytes were altered. An excellent discussion of similar cases by Fraenkel and Sternberg may be found in the Proceedings of the German Pathological Society for 1912. The Society recognized the intimate relationship between such "pseudoleukæmic" cases and true lymphatic leukæmia, mentioned examples where the one had progressed into the other, spoke of other cases where at autopsy the two conditions were indistinguishable, and concluded that the term "pseudoleukæmia" was superfluous and should be abandoned. Two cases with leukæmic blood pictures showed at autopsy infiltration of the parenchymatous organs and bone marrow but a sharp limitation of lymphoid hyperplasia to the mesenteric and retroperitoneal glands. Nine cases with leukæmic blood, general hyperplasia of lymphoid tissue, and infiltration of parenchymatous organs and bone marrow, were quite typical. One case observed for over three years gradually developed large invasive tumor masses of the inguinal and retroperitoneal glands.

#### LEUKOSARCOMA

Leukosarcoma was used by Sternberg to designate a group of cases characterized by a leukæmic blood picture and an invasive lymphoid tumor. The origin of this tumor, neoplastic in nature, might be anywhere—breasts, skull, mediastinum. The blood picture, according to him, is not that of a small lymphocytic leukæmia but shows a high percentage of large lymphoid or "leukosarcoma" cells. Helly apparently goes further by differentiating leukosarcoma (a true neoplastic tumor) according to its association with "lymphopenia, sublymphæmia, or lymphæmia." On the other hand, Türek and Naegeli believe that leukosarcoma is only a stage of lymphatic leukæmia.

Four cases taken from the autopsy records of The Johns Hopkins Hospital and 22 cases collected from the literature were summarized. From this study it was possible to derive a more precise knowledge of the clinical course and pathology of this group and more accurately to discuss its relationship with allied conditions: (1) In 24 cases (92 per cent) the disease occurred in young individuals between the age of 7 and 30 years. (2) Loss of weight, malaise, chest symptoms, and glandular swellings, are prominent symptoms. (3) Leukæmic blood, lymphoid in type, large liver and spleen, general glandular enlargement with a tumor mass in the mediastinum or elsewhere may be looked for clinically. (4) The disease runs an acute course; 25 (96 per cent) of the 26 patients died within one year after the onset. (5) At autopsy the findings

are characteristic and may be summarized as follows: (a) General glandular enlargement (85+ per cent); (b) infiltration of parenchymatous organs (100 per cent) and bone marrow; (c) an invasive mediastinal tumor spreading more or less to pleura, diaphragm and pericardium, in 21 cases, (84+ per cent); (d) microscopically, uniform extensive infiltration of lymphoid cells, measuring 5-6  $\mu$  in diameter, with little cytoplasm and a nucleus containing coarse chromatin granules. Mitotic figures may or may not be present.

#### HODGKIN'S DISEASE

Twelve cases of Hodgkin's disease, taken from the autopsy records of The Johns Hopkins Hospital, have been reviewed. Nine cases are typical examples of Hodgkin's disease as described by Reed and Ziegler. They all presented general glandular enlargement with involvement of liver and spleen. Tuberculosis was present in two cases; three cases showed invasive tumor masses associated with the mediastinal or cervical glands. Microscopically, (1) alteration of the normal architecture, (2) appearance of lymphoid cells, (3) decrease in normal lymphocytes, (4) increase in connective-tissue stroma, (5) and diffuse endothelioid hyperplasia with large irregular mononuclear and polynuclear giant cells, were constant. Eosinophiles were present in three cases. Three acute cases subjected to radium, difficult to classify, showed at autopsy a general glandular enlargement with involvement of liver and spleen. Lymphoid cells predominated. The total number of cells was not decreased, the stroma was not conspicuous. A few endothelioid cells and giant cells and phagocytes were noted.

#### DISCUSSION

From the foregoing summary of cases it seems possible to draw a number of interesting observations.

First of all, I wish to emphasize the close relationship between leukosarcoma, lymphosarcoma, and lymphatic leukæmia. Three leukosarcoma cases studied in The Johns Hopkins Department of Pathology, presented a blood picture of lymphatic leukæmia, general involvement of the lymphatic system, infiltration of the parenchymatous organs and bone marrow, associated with an invasive mediastinal tumor. One case beginning as a localized tumor of the chest developed a typical lymphatic leukæmia after X-ray treatment. The glands were enlarged all over the body, the liver and spleen descended below the costal margin. The subsequent findings at autopsy were similar to those in the cases mentioned above. It seems, then, that leukosarcoma combines the features of lymphosarcoma and lymphatic leukæmia and that a localized lymphosarcoma may under certain conditions become generalized and, with a blood picture of lymphatic leukæmia, may terminate as a leukosarcoma. Very important in this connection is the mode of spread of the lymphosarcoma group which, regardless of its primary site, extends in a characteristic manner first by local infiltration and later by the blood stream to parenchymatous organs, lymph glands, bone marrow, etc. At this stage only the negative blood findings differentiate the case from leukosarcoma and only the blood and the presence of

a local infiltrating mass differentiate it from lymphatic leukaemia. Finally, in lymphatic leukemia one may see a similar mode of progression. The first cases, showing no increase in the number of blood lymphocytes, presented at autopsy hyperplastic lymphoid tissues with generalized infiltrations. Other cases, with a positive blood picture, showed more or less localized lymphoid involvement. The main group is quite typical but the last case developed, during the course of the leukaemia, large infiltrating masses in the inguinal regions. It appears, then, that in the leukaemia group some cases closely resemble certain types of lymphosarcoma, while others approach leukosarcoma.

Microscopically, the lymphocytic infiltrations of the organs in these diseases differs in quantity but not in quality. Distant lymph nodes appear the same in leukosarcoma as in lymphosarcoma and leukaemia. The parenchymatous organs and even the bone marrows are indistinguishable. Although the size and shape of the cell varies in the several cases it still retains its lymphoid character.

It appears not unlikely, then, that leukosarcoma, lymphosarcoma and lymphatic leukemia are different manifestations of the same disease. In early life the primary focus may be in the small intestine or mediastinum. The disease then runs a rapid and fatal course spreading locally or generally (lymphosarcoma), occasionally to terminate with manifestations of lymphatic leukaemia (leukosarcoma). Later in life the focus may be anywhere and the course is more protracted. Extension, however, occurs in a similar manner. In many ways the disease is quite comparable with tuberculosis which in the young localizes in the chest or intestines, later to become spread more diffusely, and in adult life assumes many odd forms, attacking the kidney, uterus, skin, etc.

Next, I wish to say a word about the nature of this disease. From the preceding paragraph it may be seen that its local manifestations and mode of spread are not at all comparable to a malignant tumor with its metastases but simulate more closely the progress of an infectious disease. The site of origin is determined by an infiltrating mass of lymphoid cells not in themselves destructive but merely pushing aside normal tissue elements. Its mode of spread as a diffuse periportal infiltration, accumulation about the Malpighian bodies, scattered cells separating normal kidney tubules and glomeruli, homogeneous collections of cells in the bone marrow and other tissue, certainly does not find its parallel in the biology of any known tumor.

From unpublished observations by W. H. Lewis and L. T. Webster upon the activities of lymphocytes in tissue cultures (normal, tuberculous, lymphosarcomatous, Hodgkin's, and leukaemic lymph glands were cultured and the activity of the lymphocytes was studied), the following points may be valuable: (1) The lymphocyte in normal and pathological lymph nodes, observed in tissue cultures, is actively amoeboid at body temperature and migrates, proceeding in a definite and characteristic manner for several days. (2) It probably responds to various chemical and bacterial substances. From the observation of many fixed sections from autopsies in which the lymphocytes, elongated and spindle-

shaped, were similar to those in cultures and from experiments by Murphy it seems altogether probable that amoeboid activity may take place on the part of the lymphocyte *in vivo*.

This lymphoid infiltration, then, variously designated as leukosarcoma, lymphosarcoma, and lymphatic leukaemia, may be best explained as a response to some chemotactic agent derived from a living organism. So long as this substance remains confined, the accumulation of lymphocytes is local but the presence of this substance in any part of the body, parenchymatous organs, glands, bone marrow, etc., produces in that area an infiltration of lymphocytes.

A minor point of some prognostic significance might be mentioned at this time. Several clinical cases where a lymph node had been removed for diagnosis showed microscopically evidence of amoeboid activity on the part of the lymphocytes. All of these cases, 12, died within a few months.

Hodgkin's disease, a reticulo-endothelial cell proliferative process, in contrast to leukosarcoma, lymphosarcoma, and lymphatic leukaemia, which are lymphocytic proliferative processes, may be diagnosed microscopically and is probably a distinct entity.

Clinically, until a definite etiological agent has been discovered, these conditions will remain little more than diagnostic problems. From the study of 26 clinical cases of lymphosarcoma and 33 cases of Hodgkin's disease in which a lymph gland had been removed for examination, it seems that lymphosarcoma cannot always be diagnosed microscopically, and that in early cases it is unwise to give a certain prognosis. Hodgkin's disease, on the other hand, may be diagnosed from the microscopical examination of a single gland and a definite prognosis may be offered. Seven atypical cases in this series, however, the patients being alive and well from 2 to 11 years after examination, appear quite similar microscopically. The more or less homogeneous mass of lymphoid cells suggests some benign form of chronic lymphadenitis. Associated with these cases is frequently a so-called transient "infectious mononucleosis" in the blood characterized by an increase in the number of lymphoid cells.

#### CONCLUSIONS

1. It seems probable that lymphosarcoma, lymphatic leukaemia, and leukosarcoma, are different manifestations of the same disease.
2. The term "lymphadenosis, leukaemic or aleukæmic" would express this idea and simplify the classification until a definite etiological agent is found.
3. This disease is not a neoplasm but a direct response on the part of lymphocytes to a chemotactic influence exerted by the disease-causing agent. The presence of this substance in any tissue or organ produces there a local accumulation of lymphoid cells.
4. Diagnosis and prognosis of this disease in its early stage is difficult from the microscopical examination of a single gland because of its resemblance to certain types of benign lymphadenitis.
5. Evidence of amoeboid activity, on the part of the lymphocytes, is indicative of a rapid fatal course.

6. Hodgkin's disease, a distinct entity, may be diagnosed and accurately prognosed from the microscopical examination of a single gland.

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SOME ADAPTIVE DIFFICULTIES FOUND IN SCHOOL CHILDREN<sup>1</sup>

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In the winter of 1916 and 1917 the Joint Committee on Education, of Chicago, invited a discussion in the interests of their public schools by representatives from the fields of biology, psychology, psychopathology and sociology. The contributions of these sciences were presented, respectively, by Herbert S. Jennings, John B. Watson and Adolf Meyer of The Johns Hopkins University and by William I. Thomas of the University of Chicago. The trend of these suggestions, derived independently from experience and research, lies in the direction of emphasis on the study of the individual child and his needs, rather than on the reference of the individual to a group.

In his paper entitled "Mental and Moral Health in a Constructive School Program" Dr. Meyer suggested that "a school physician with training in psychopathology attend regular conferences at which the management of problematic pupils is discussed," and arrange for the study with teachers and parents of any case recommended for special attention. The practical application of this idea was begun by the writer January, 1918, in Public School No. 76, which lies in the Locust Point District of Baltimore, previously reported on by Dr. C. M. Campbell (*Mental Hygiene*, Vol. 2, pp. 232-244). The 15 school months during which this study was made were interrupted by no less than three enforced school holidays of from two to eight weeks each, due to the influenza epidemic, plumbing tragedies and the burning of the main school building. These circumstances, together with the fact that only two days a week were devoted to this work, may comfort those who mourn that only 46 children were studied during the above period.

Requests for suggestions in regard to specific children were more than it was possible to compass. They came from the kindergarten to the eighth grade with a breadth of distribution exceeded only by the diversity of the individual complaint. Of the 46 children coming under observation 35 were reported as having difficulty in keeping up with their grade in one or more subjects. In each case where there was a question of retardation the Binet-Simon tests were applied. As a result 16 of the above mentioned 35 were found to have a mental

retardation of from three to six years. The academic troubles of the remaining 19 retarded children were associated with, if not the disguised expression of, such faulty psycho-biological reactions as shyness, laziness, inattention, vicious tendencies, sensitiveness to criticism, day dreaming, hypochondriacal fears, etc. The 11 remaining from the total of 46 were referred for more overt adaptive difficulties of temper tantrums, sullenness, crying spells, twitching, indifference, excitability, poor co-ordination with the hands, quarrelsomeness, etc.

So familiar are the majority of such reactions in the world of every day that one hardly pauses to consider these facts. They seem to be the vague result of still vaguer causes. Faulty nutrition, inadequate exercise, the strain of defective light and ventilation, a poorly balanced school curriculum mustering under the banner of science, figure from time to time in drives of public health and educational controversy as abstract sponsors of these unhealthy manifestations of child life. But can one study such twists of behavior and mental attitudes in terms of abstract physiology, pedagogy or "child psychology"? What are the concrete facts about the shyness, twitching, and inattention of John and Henry? Each is as distinct in the array of data of his total function as in those of his special organs. He has had his own start in birth, early development, training and home influence, as well as in sleeping, eating and other factors of so-called personal hygiene. To understand his trouble in concentration, his temptations, his impulsive behavior, his lack of satisfaction in work and play, one must have a life record of the individual child in the stories of parent, teacher, physician and child himself. The facts of history, school report, habit data and personal examination were followed in each case by suggestions for modification, and as far as possible by careful subsequent notes. The results as tabulated in the original article are encouraging in spite of the handicap of overworked teachers and unsettled times. It is interesting to note that the children who responded with improvement from, and in many instances with complete disappearance of, the adaptive difficulty for which they were referred were found below the fifth grade.

In conclusion it should be stated that these studies were not undertaken for the purpose of obtaining statistical data on the neurotic child nor yet for purposes of adding to what has already been described in regard to the psychotic constitution.

<sup>1</sup> Abstract of a paper read at a meeting of the Federation for Child Study, New York City, January 28, 1920, and published in *Mental Hygiene*, Vol. 4, No. 2, April, 1920.

That some of the material presented can readily be correlated with these syndromes is as natural as that other case material falls into the group of mentally retarded children who are the subjects of most school surveys in the interests of mental hygiene. On the contrary, this work was taken up solely with

a view of discovering some of the common adaptive difficulties of childhood, and of finding out whether one accustomed to studying sources of failure in individual human beings could be of help to parents and teachers who are baffled and perplexed by difficulties of development in their childish setting.

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#### NEW PUBLICATIONS.

The following monograph is for sale by The Johns Hopkins Press, Baltimore, Md.:

**Relation of Tonsillar and Nasopharyngeal Infections to General and Systemic Disorders.** By S. J. CROWE, S. SHELTON WATKINS and ALMA S. ROTHWOLTZ. 63 pages. Price, \$1.25.

#### ERRATA

Attention is called to a typographical error on page 365 of the October Bulletin, in the article entitled "The Coagulation Time of Citrated Plasma on Recalcination" by H. C. Gram. The second paragraph in the right hand column should read as follows:

The recalcination used is the result of experience which showed that the optimal recalcination always took place in the tubes containing 2, 3, 4 and 5 drops of a 1 per cent Cacl<sub>2</sub>, 6H<sub>2</sub>O. If instead of a 10 per cent solution a 3 per cent solution of citrate is used, the recalcination must be 1, 2, 3, and 4 drops. Cases of protracted coagulation time, where the optimal recalcination was 2 or 5 drops, were controlled afterwards with 1 or 6 drops, respectively, no errors being found.

Attention is called to a typographical error on page 107 of the November BULLETIN, in the article entitled "The Treatment of Neurosyphilis by the Intraspinal Route," by Albert Keidel and Joseph Earle Moore. Table II should read as follows:

Diagnosis	No. of cases	Clinical result		Sero-logical result	
		Good	Bad	Good	Bad
Tabes dorsalis.....	6	4	2	1	4*
General paresis.....	6	2	4	1	5
Tabo-paresis.....	2	..	2	..	2
Cerebrospinal syphilis.....	8	8	..	5	3
Asymptomatic neurosyphilis.....	3	1	2	..	3
Total .....	25	15	10	7	17

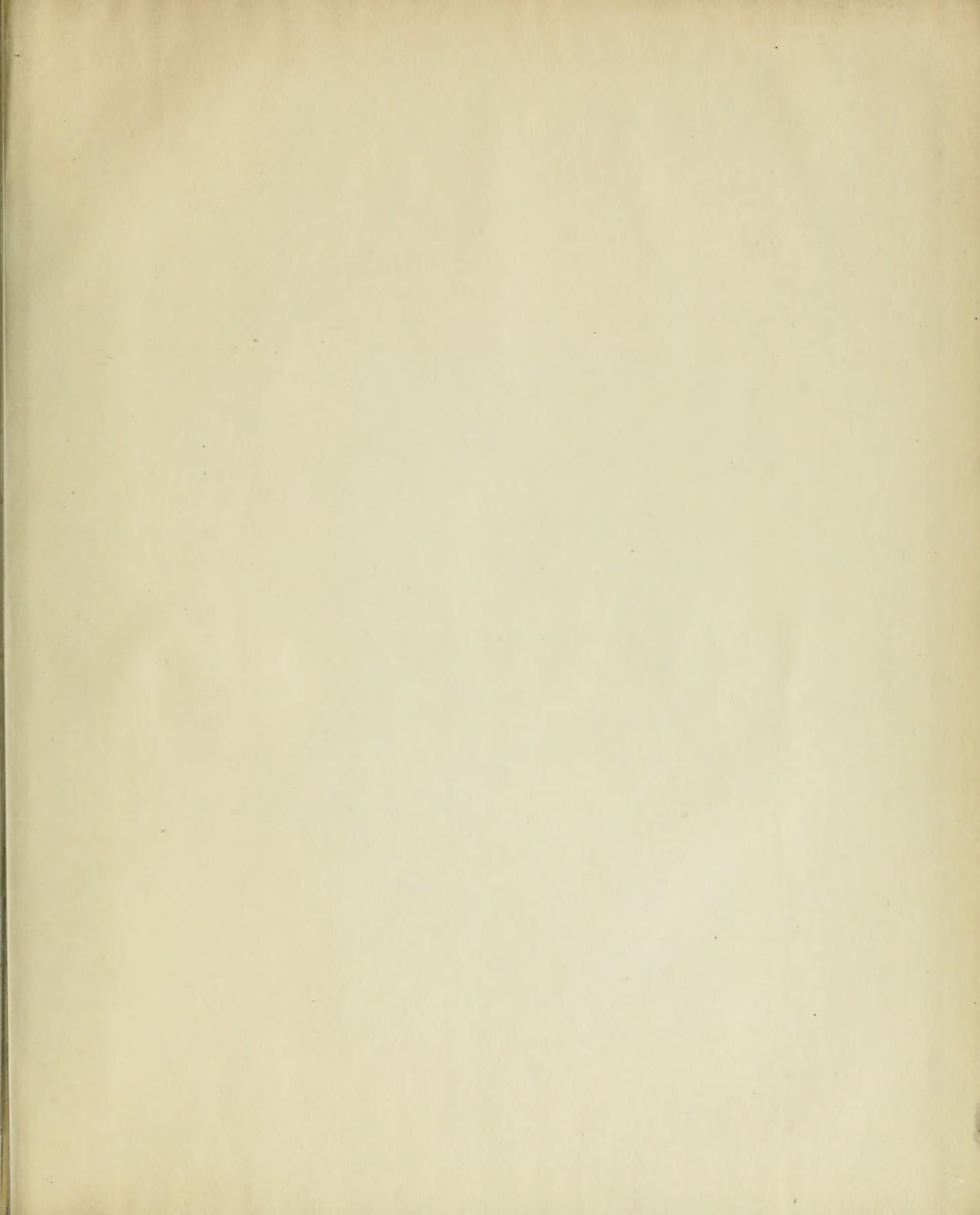
\* One case, with negative serology at the start of treatment, remained unchanged.

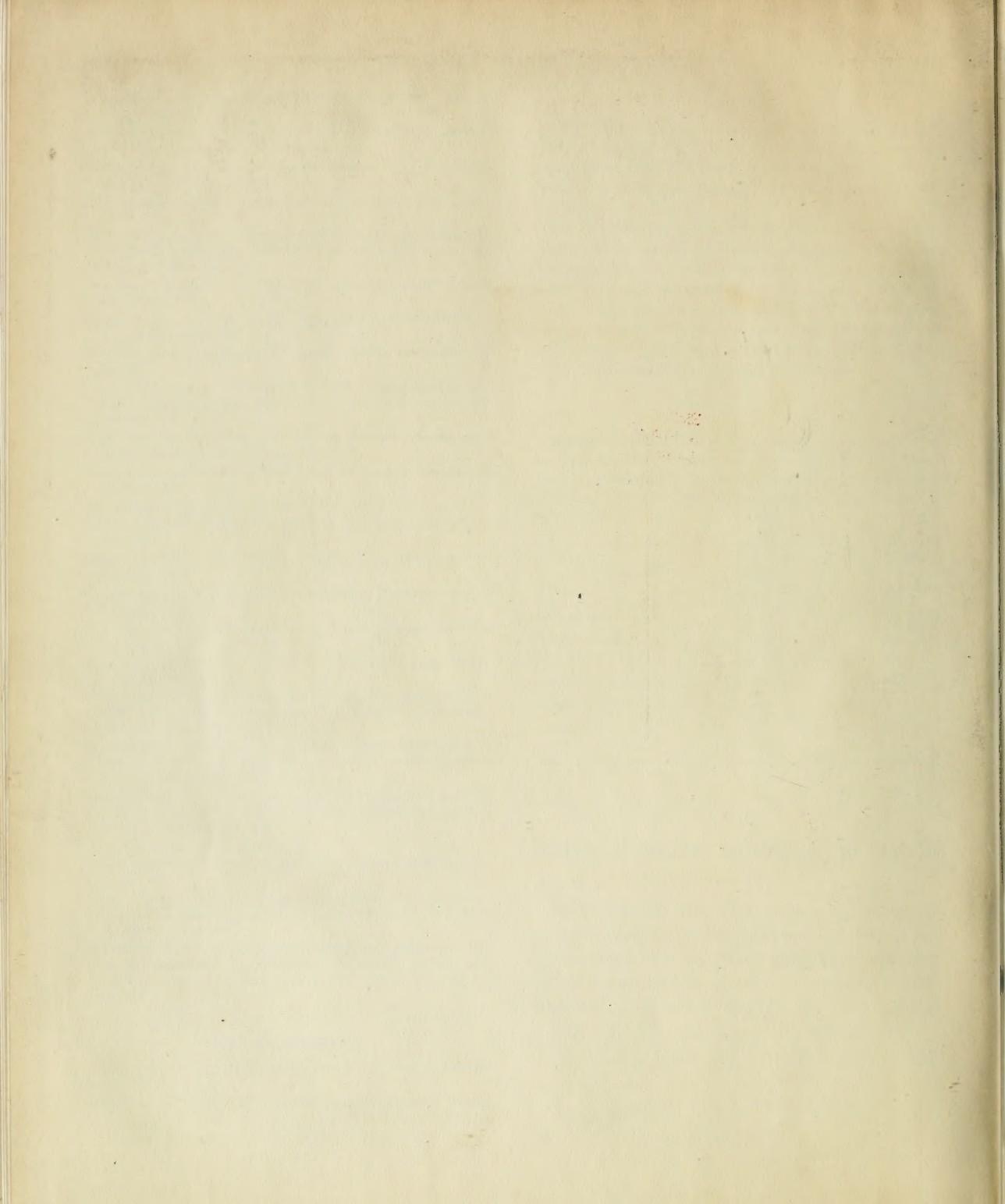
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